PRIMARY HYPEROXALURIA TYPE I

MANSOURA NEPHROLOGY CONGRESS 2016

NEVEEN A SOLIMAN
Professor of Pediatrics
Kasr Al Ainy School of Medicine
Cairo University

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nsoliman@kasralainy.edu.eg

Cairo University

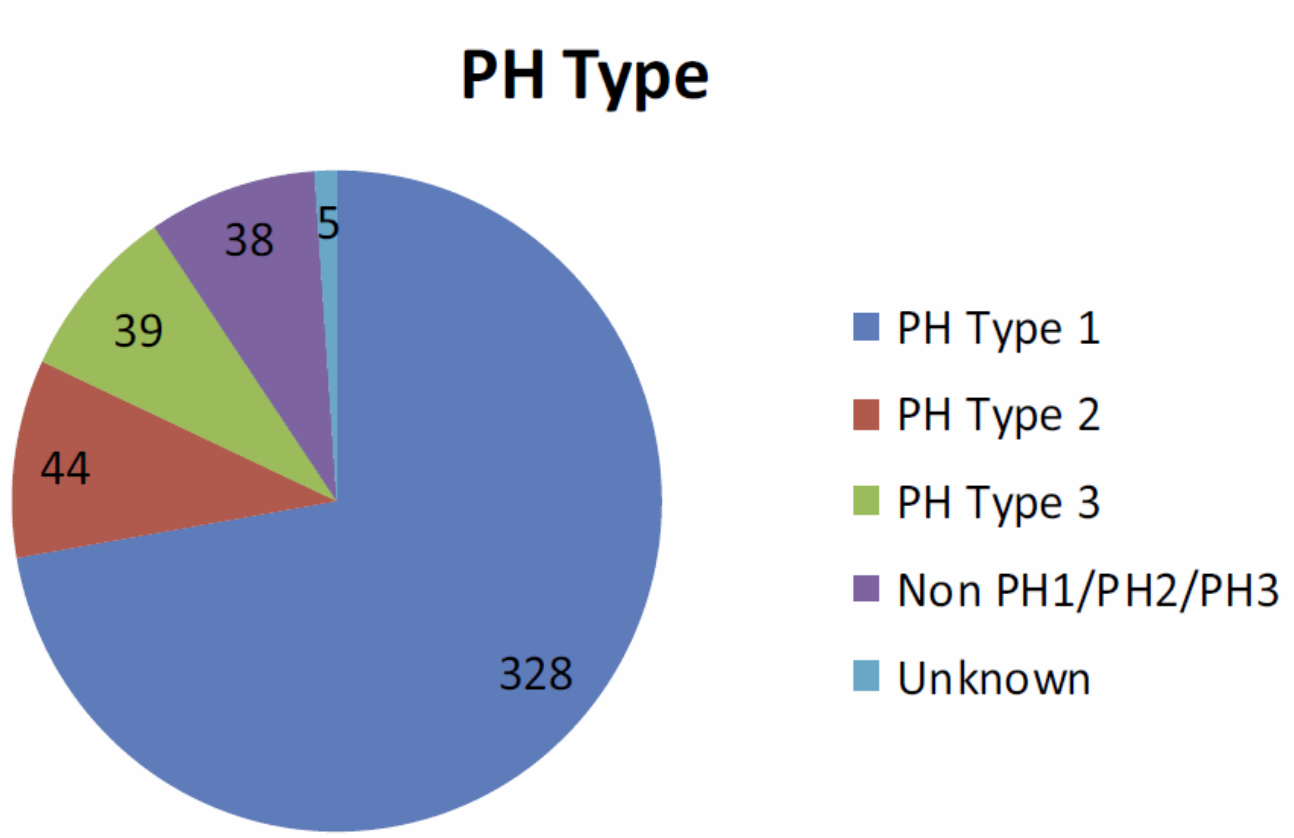
KASR ALAINY

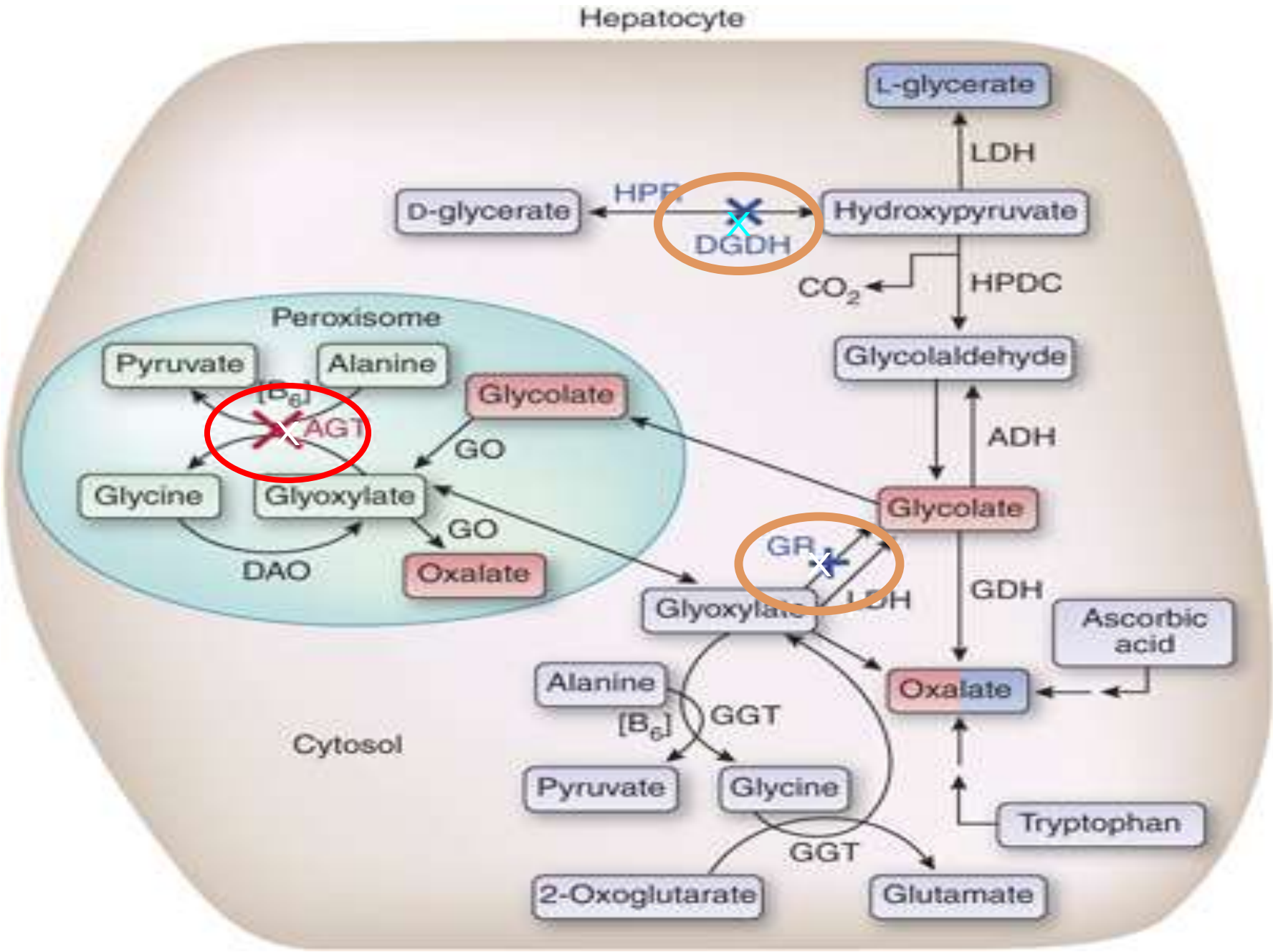
LEPOUTRE C.

1925

Calculs multiples chez un enfant: Infiltration du parenchyme rénal par des dép.ts cristallins. J Urol 1925

RARE KIDNEY STONE CONSORTIUM




Hepatocyte
L-glycerate
LDH
D-glycerate
HPR
DGDH
Hydroxypyruvate
CO_2
HPDC
Peroxisome
Glycolaldehyde
Pyruvate
Alanine
$[B_6]$
AGT
Glycolate
ADH
GO
Glycine
Glyoxylate
Glycolate
GO
GR
DAO
Oxalate
GDH
Ascorbic acid
Alanine
Oxalate
$[B_6]$
GGT
Cytosol
Pyruvate
Glycine
Tryptophan
GGT
2-Oxoglutarate
Glutamate


WHY?

Table 2. Features and Treatment of the Inherited Primary Hyperoxalurias.

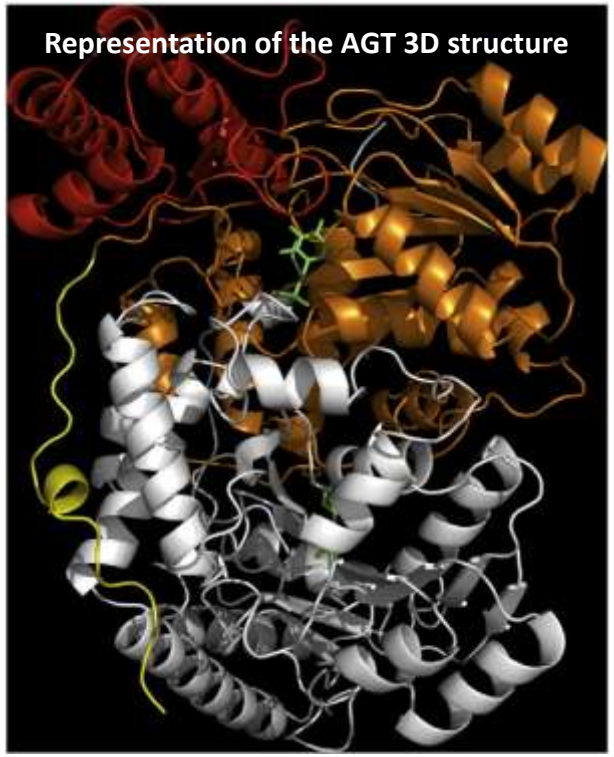
Feature	Type 1	Type 2	Type 3
Chromosomal location	2q37.3	9p13.2	10q24.2
Age at onset	All ages, although mostly in childhood	All ages	All ages
Presentation	Calcium oxalate renal stones, nephrocalcinosis, renal failure	Calcium oxalate renal stones	Calcium oxalate renal stones
Treatment			
Supportive treatment	Hydration, citrate, pyridoxine	Hydration, citrate	Hydration, citrate
Transplantation	Liver and kidney	Kidney	Not required — no reported cases of renal failure to date

Cochat & Rumsby, NEJM 2013

Primary hyperoxaluria type I

- AR, MIM #259900

- Deficiency of the liver specific, peroxisomal, pyridoxal phosphate-dependent enzyme alanine : glyoxylate amino transferase (AGT) leading to hyperoxaluria, progressive renal involvement, and subsequent systemic deposition of calcium oxalate (Caox)

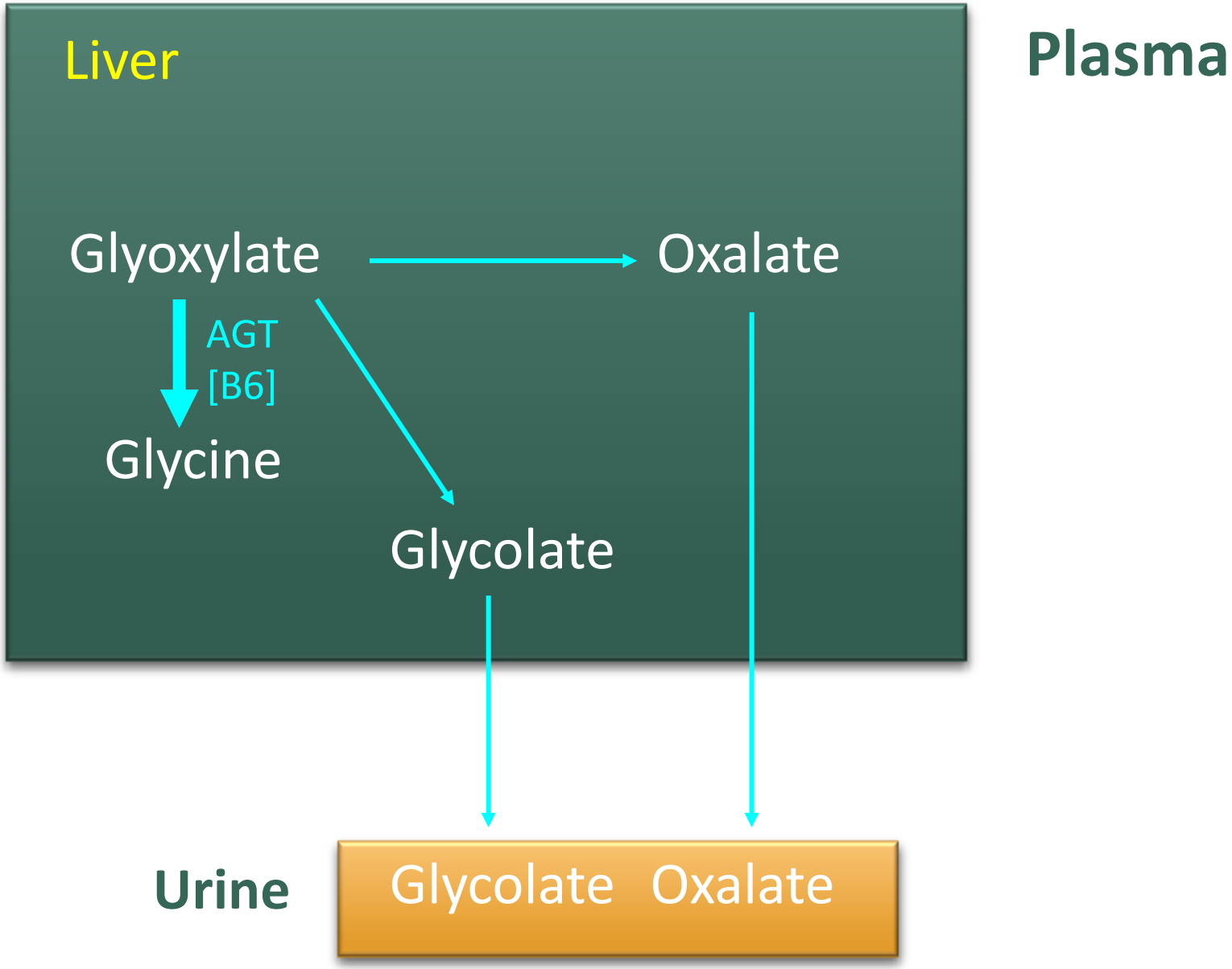


- Lack of familiarity with PHs
- Heterogeneous clinical expressions
- Diagnostic delay ESRD!

- Knowledge of the spectrum of disease expression
- Early diagnosis/initiation of treatment before renal failure

HIGH INDEX OF CLINICAL SUSPICION

Healthy


Liver
Plasma
Glyoxylate
Oxalate
AGT
[B6]
Glycine
Glycolate
Urine
Glycolate Oxalate

Healthy

Liver

Glyoxylate → Oxalate

Glyoxylate ⇢ Glycine

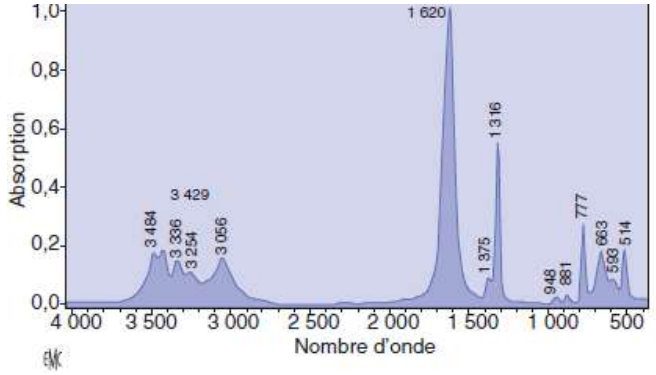
Glyoxylate → Glycolate

Glycolate → Urine

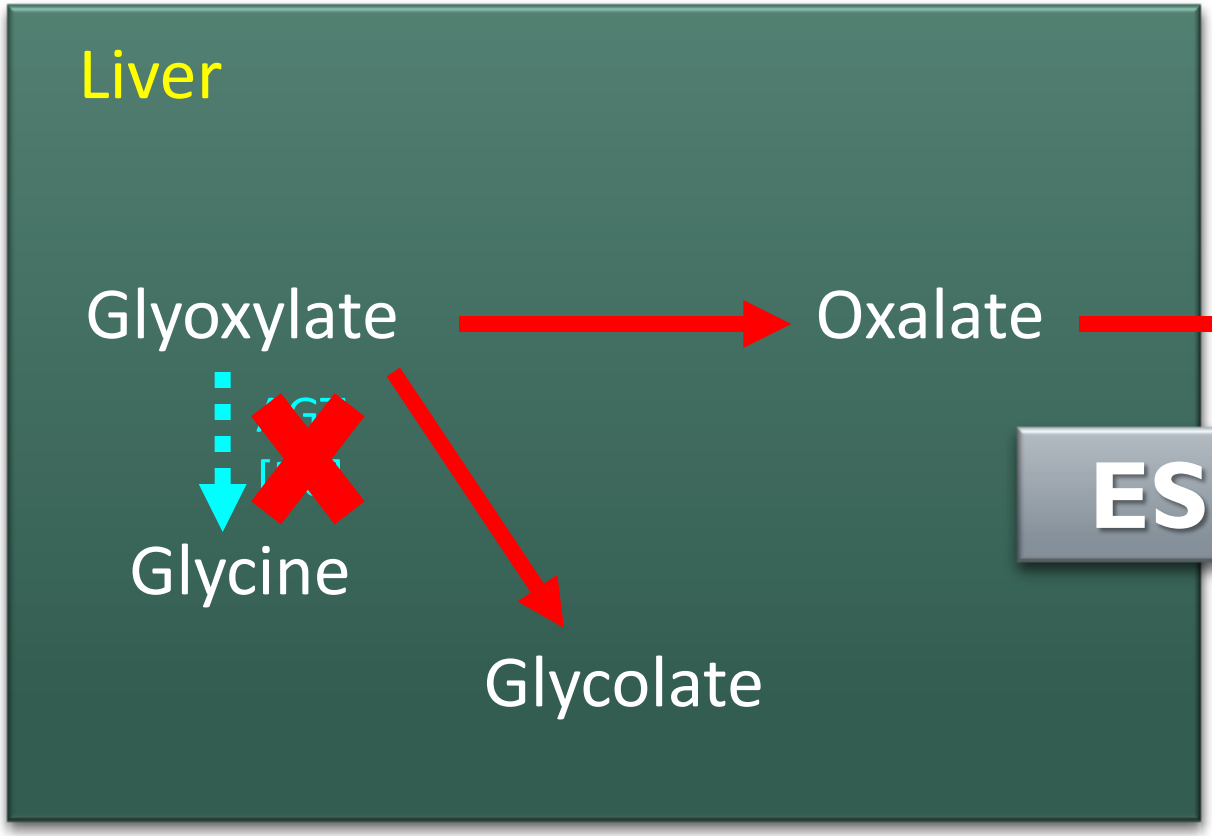
Oxalate → Urine

Urine: Glycolate Oxalate

Plasma



Healthy

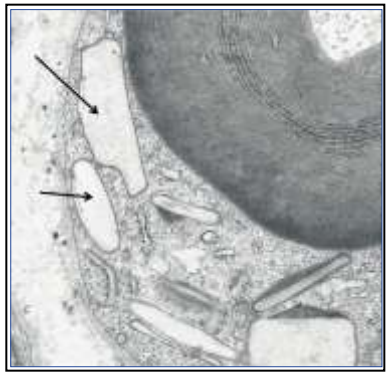


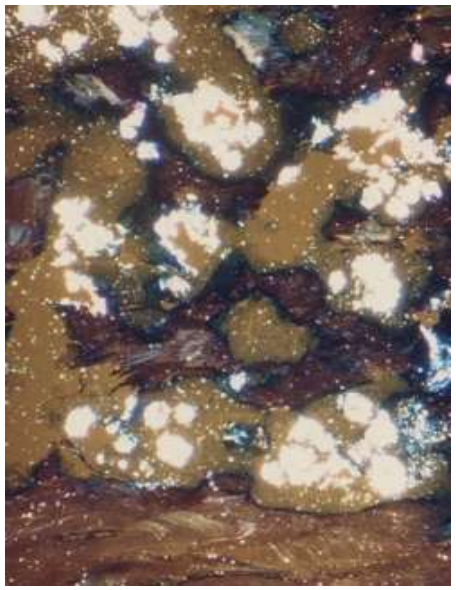
Plasma

ESRD

Bones

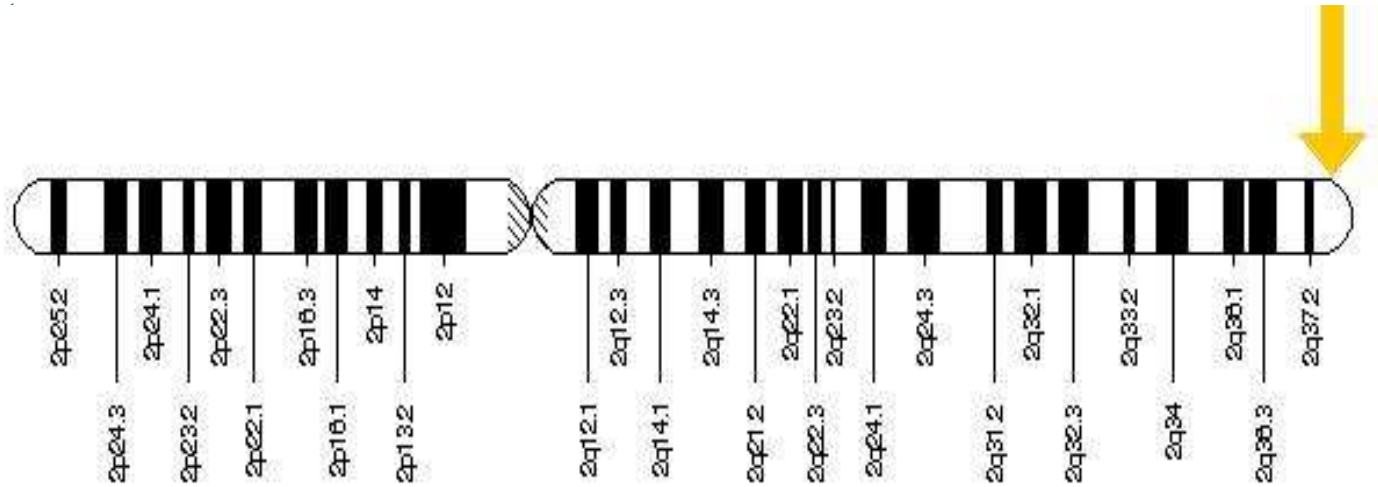
Oxalate





Primary hyperoxaluria type I

- The ***AGXT*** gene is located on chromosome 2 (2p37.3)
- First symptoms:
  - in 15% before one year of age
  - In 50% before five years



Primary hyperoxaluria type 1

- Prevalence ranging from 1:3 per million
- Estimated incidence rate of ~1:100 000 live births per year in Europe
- ESKF before 15 years in half of the cases $\Rightarrow$ oxalosis
- PH accounts for ~1% of paediatric end-stage renal disease (ESRD) in registries from Europe, USA and Japan

PHI IN NUMBERS

Prevalence 1:3 per million

1:100 000 live births per year

~1% of pediatric ESRD in Europe, USA and Japan

~10% in North African and Middle Eastern consanguineous nations

PHI IN NUMBERS

Onset from birth to the 6th decade of life

Median age of onset 5.5 years

20-50% of patients have advanced CKD or ESRD at diagnosis

5 yr patient survival rate after RRT is 76% vs. 92% in other ESRD patients

Risk of death in PH1 is 3 folds

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PHI IN NUMBERS

Post-Tx diagnosis in **10%** of patients

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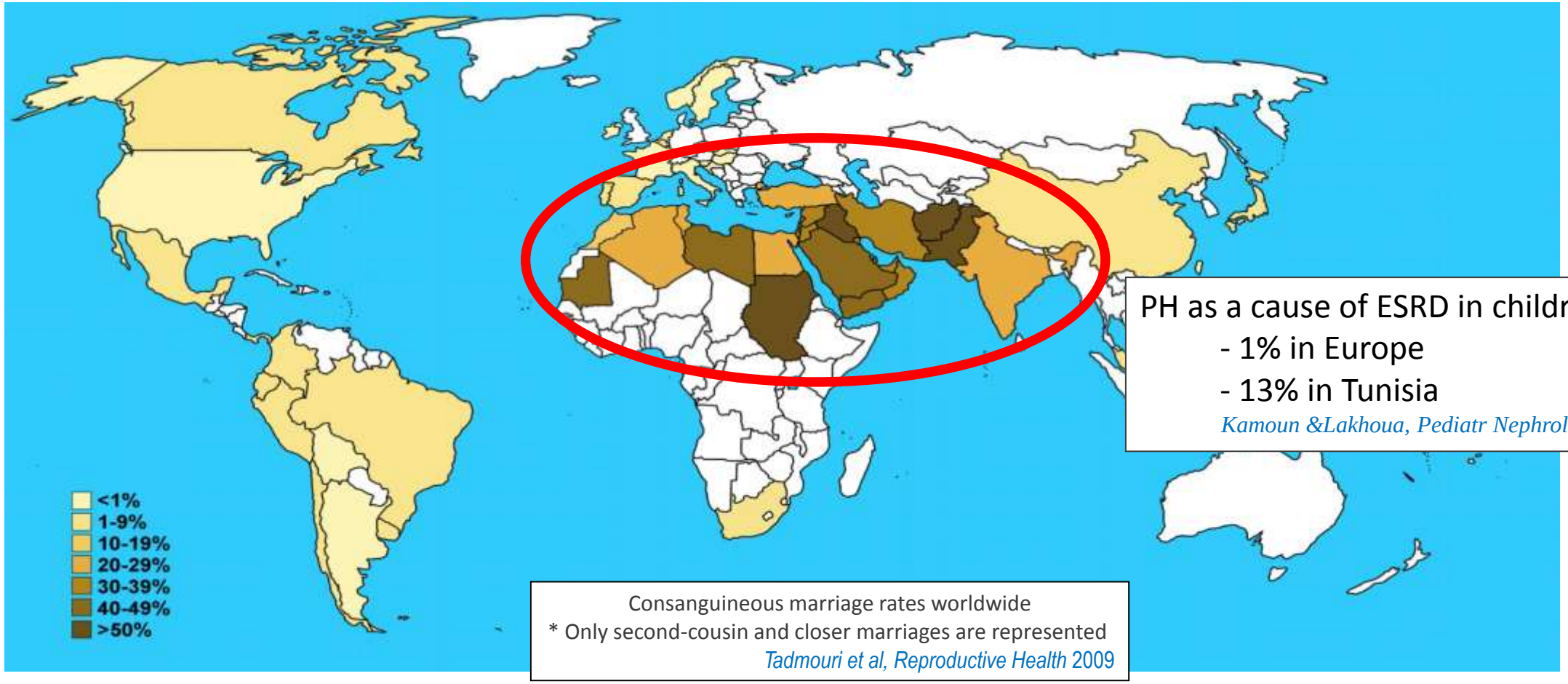
PRESENTATION

35%	Infantile form
25%	Recurrent stones with progressive CKD
15%	Late adulthood onset
15%	Presymptomatic diagnosis from pedigree screening
10%	Diagnosis from post-renal Tx recurrence

MAJOR ISSUES IN DEVELOPING NATIONS WITH HIGH RATE OF CONSANGUINITY

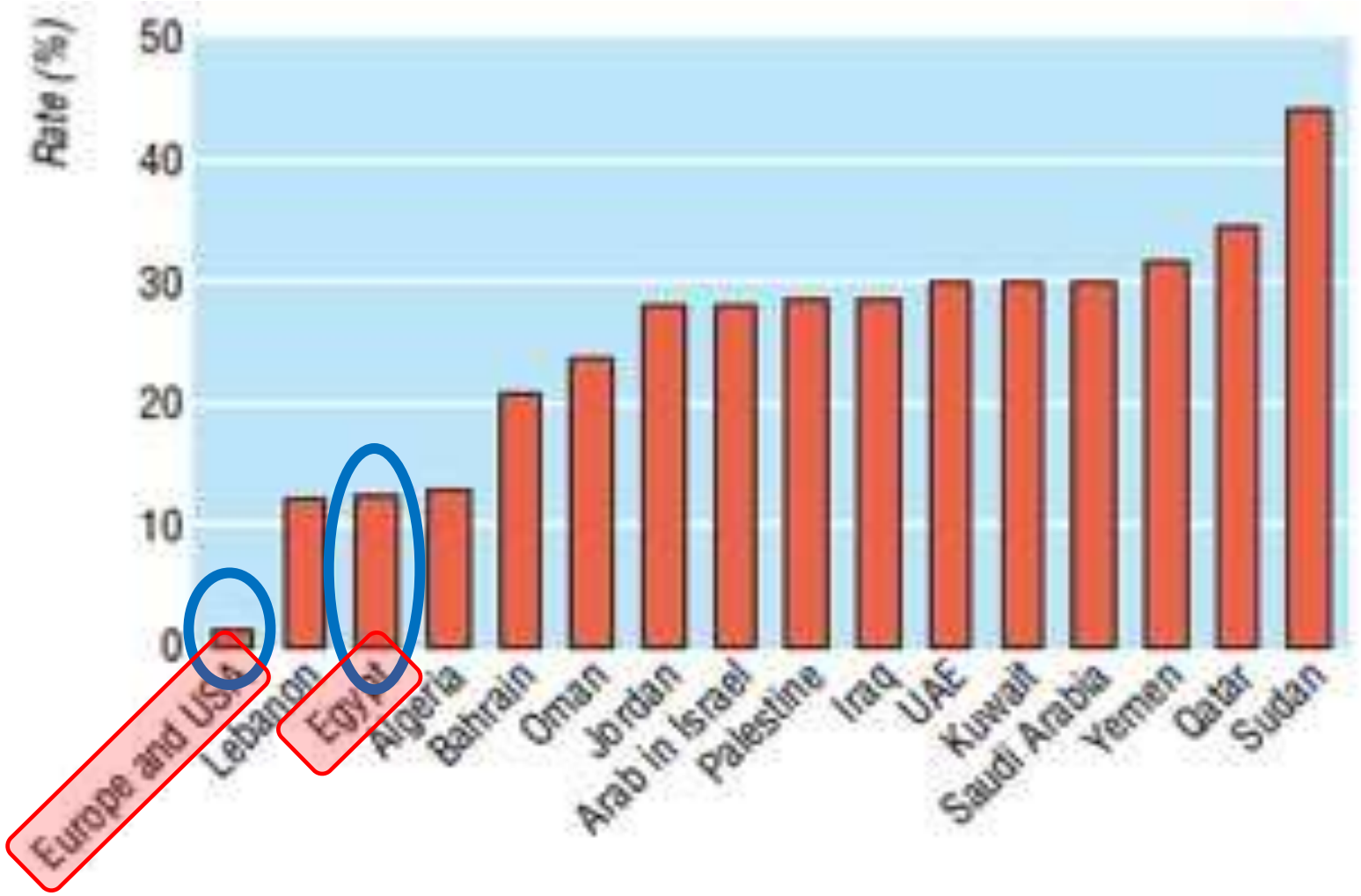


Consanguineous marriage rates worldwide
* Only second-cousin and closer marriages are represented
Tadmouri et al, Reproductive Health 2009

PH as a cause of ESRD in children
- 1% in Europe
- 13% in Tunisia

Kamoun &Lakhoua, Pediatr Nephrol, 1996

Average rates of marriages between first cousins among Arabs



Is PH I

OVERLOOKED

in Egypt?

♥*EGORD* is committed to the identification, and treatment of rare renal disorders through programs of:

- ♥Awareness
- ♥Support
- ♥Education
- ♥Research
- ♥Advocacy.

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Help us to tackle rare devastating diseases which claim the lives of children so we can change the face of rare renal diseases in Egypt

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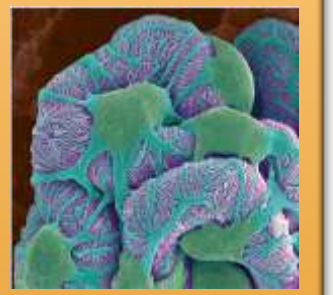
Podocytes



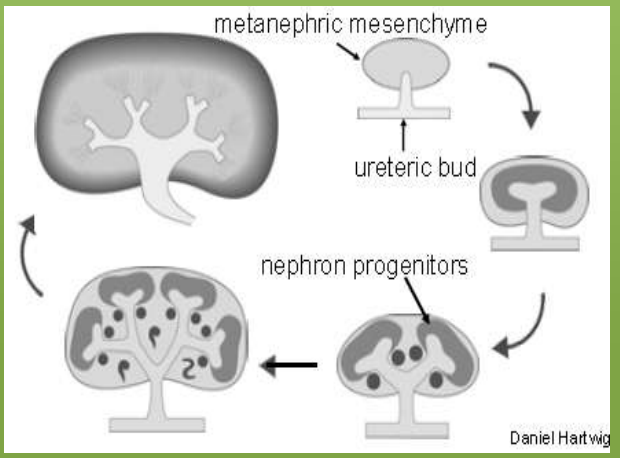
Cilia

Inherited nephrolithiasis

(PH, Cystinuria)

Cystinosis

CAKUT



When should we suspect PH1?

Primary hyperoxaluria type I

- Frequent recurrent nephrolithiasis
- Nephrocalcinosis
  - In older children or adults: CM regions
  - In infants: diffuse with few if any observable discrete stones.
- ESRD with a history of renal stones or calcinosis
- Stone composition of pure calcium oxalate monohydrate (whewellite).

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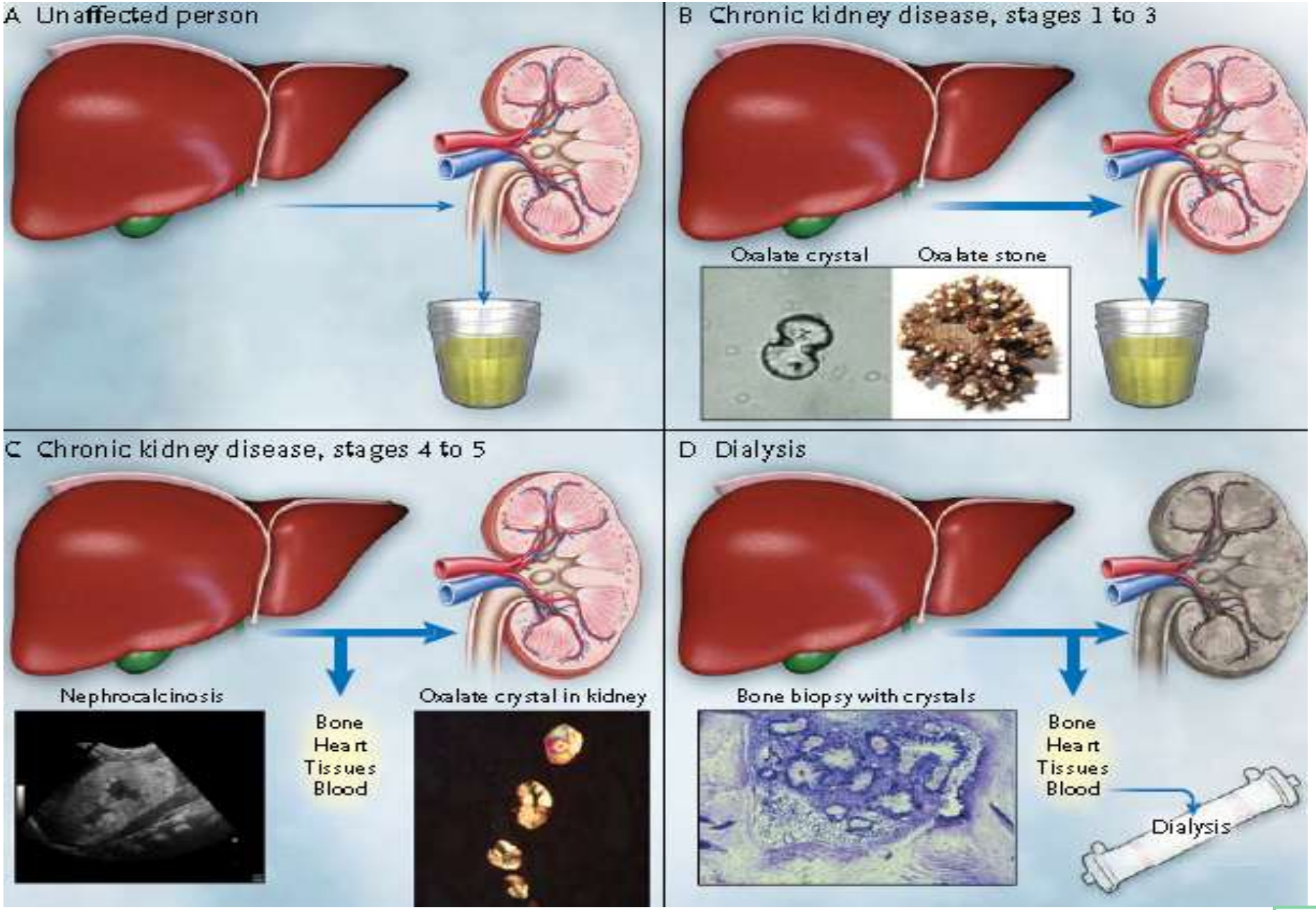
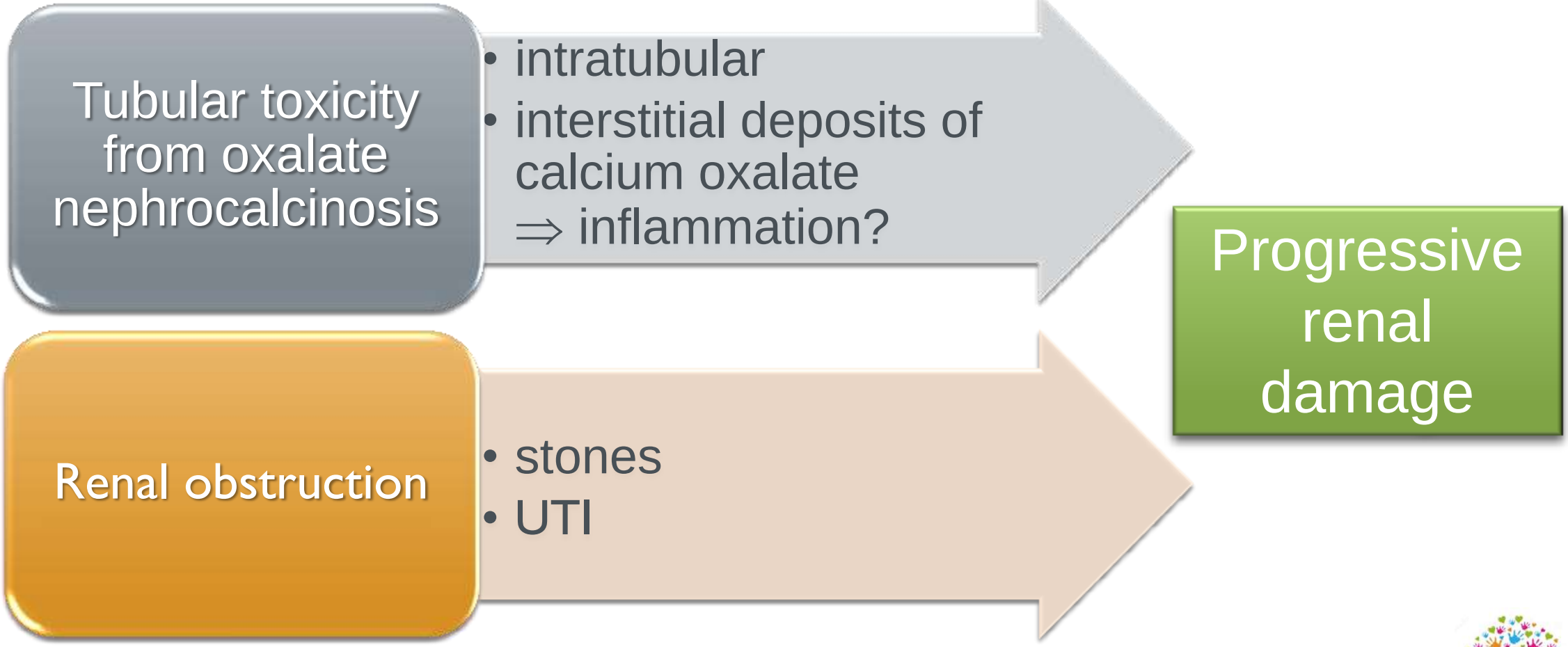
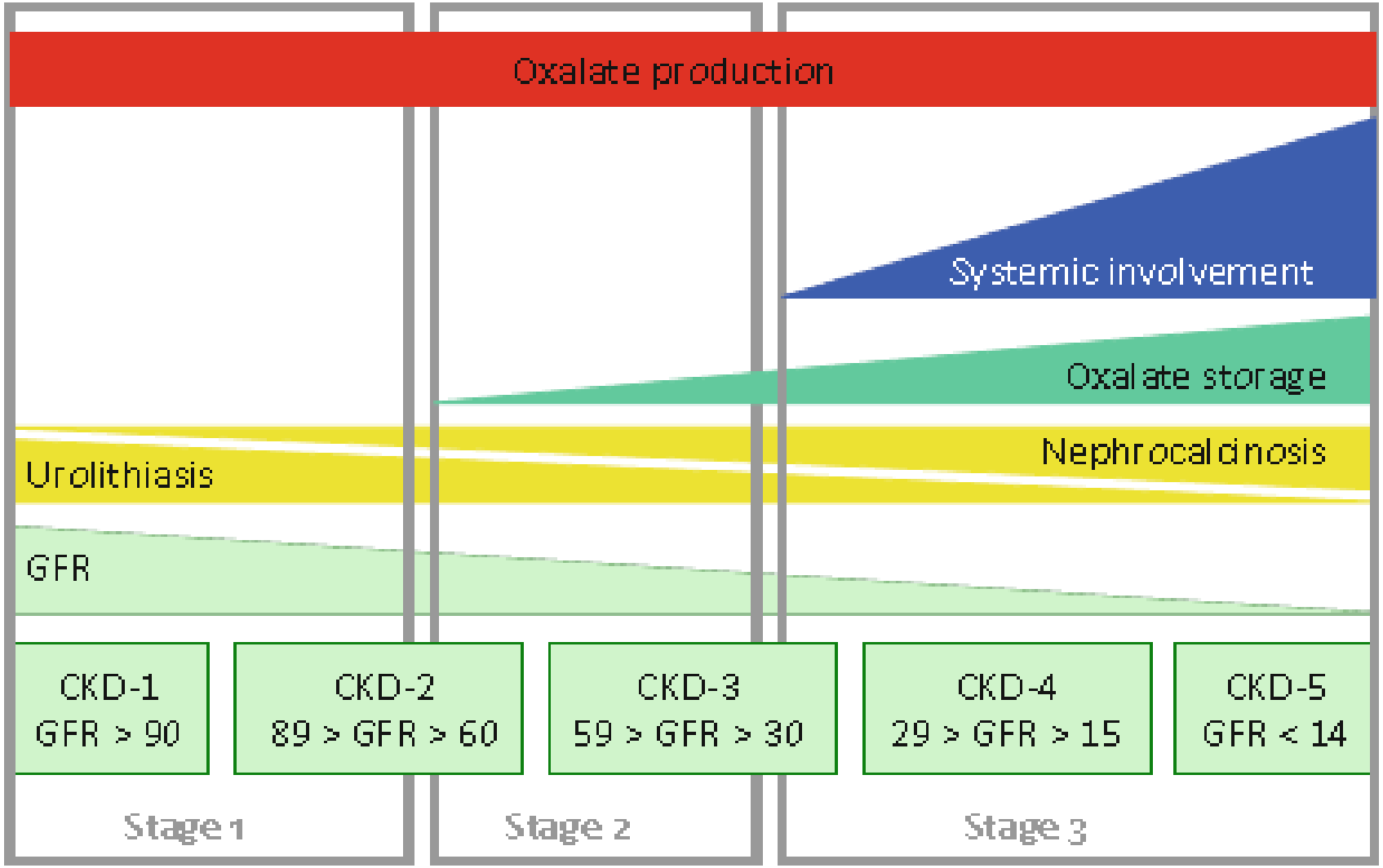


Cochat & Rumsby, NEJM 2013

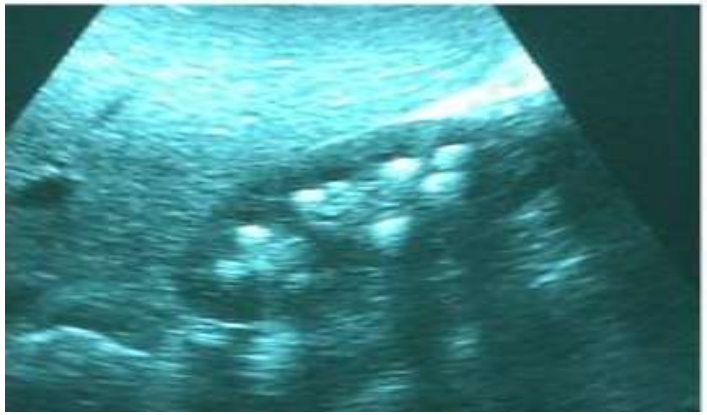

Tubular toxicity from oxalate nephrocalcinosis
• intratubular
• interstitial deposits of calcium oxalate
⇒ inflammation?
Renal obstruction
• stones
• UTI
Progressive renal damage

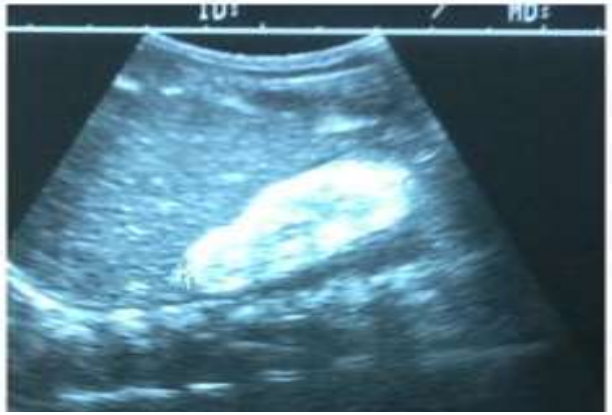
PH1: SIMPLIFIED GLOBAL COURSE OF THE DISEASE



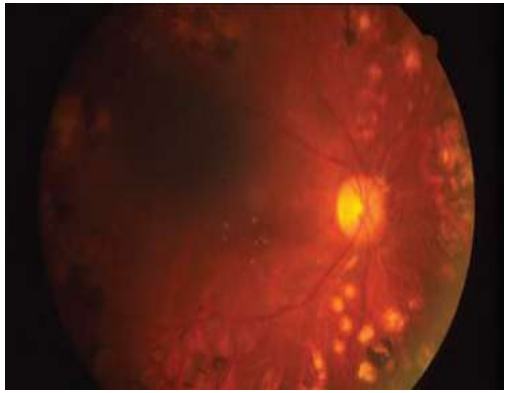
Clinical phenotype

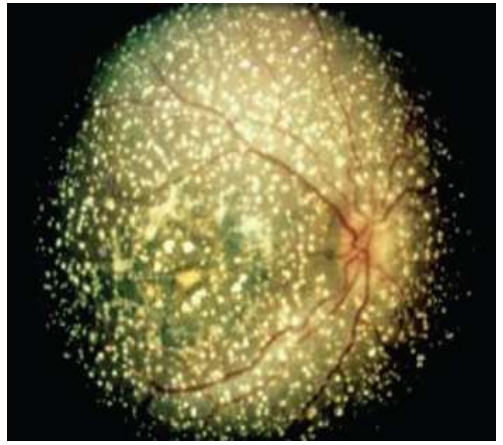
I. Renal phenotype





II. Extrarenal phenotype





Clinical phenotype

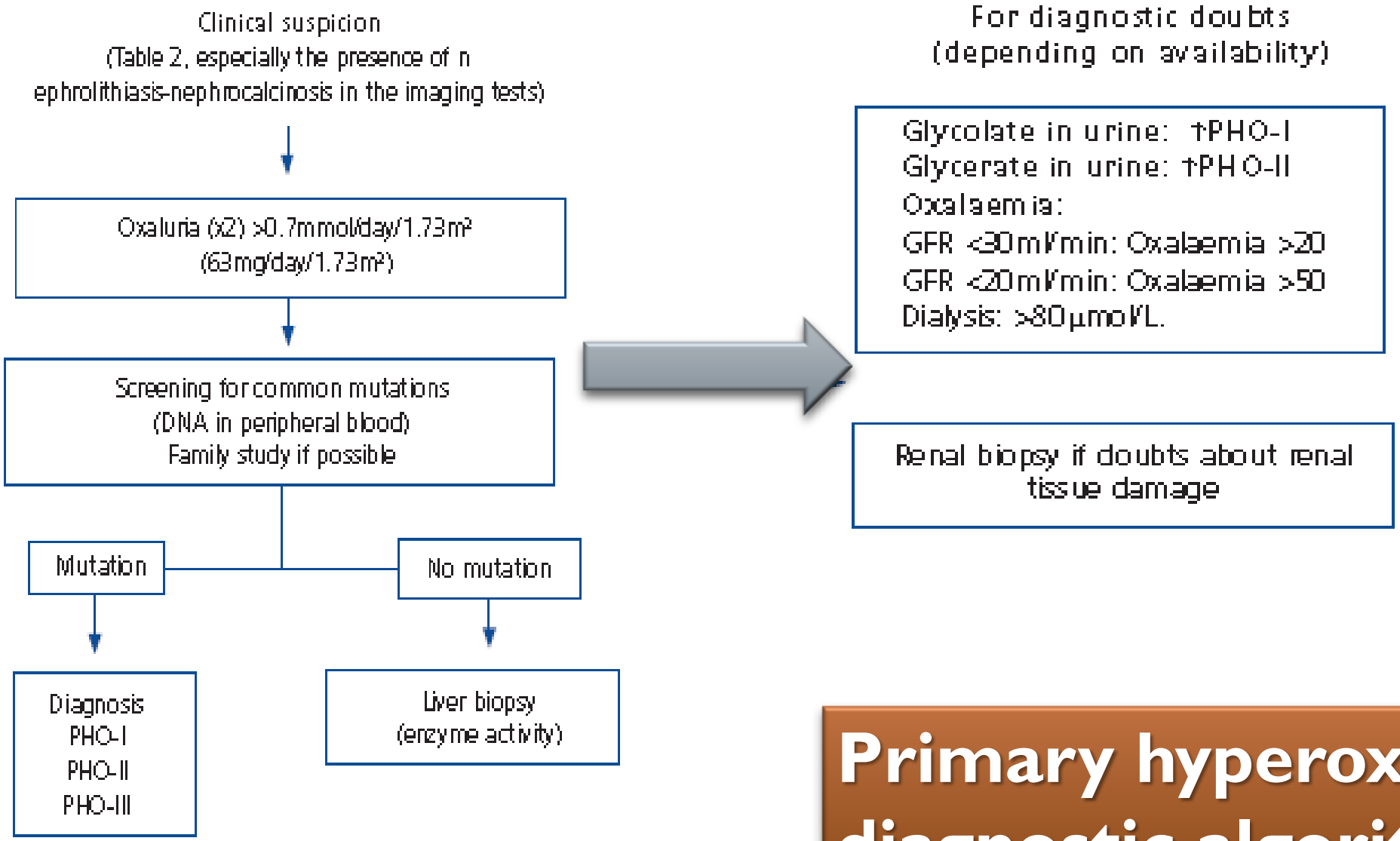
Table 1. Organ involvement in PH patients with renal failure[1]

Organ	Symptoms	Diagnosis
Kidney[b]	Stones, medullary or diffuse nephrocalcinosis, cortical nephrocalcinosis	US CT (cortical nephrocalcinosis may be missed on US)
Bone[c]	Fractures, bone pain, growth retardation	X-ray: dense or lucent metaphyseal bands at the growth cartilage plate, vertebral condensations, osteopenia, epiphyseal nuclei (target-like) knee epiphyses
Eye[c]	Disturbed vision, specific brown coloured retinal deposits	Fundoscopy
Arteries[d]	Media calcifications	US, CT
Myocardium[d]	Cardiac failure, arrhythmia, heart block, left ventricular hypertrophy, systolic and diastolic dysfunction	ECG, echocardiography CT: calcifications
Thyroid[d]	Hypothyroidism	US Thyroid function tests
Skin[e]	(Painful) skin nodules, skin necrosis, gangrene, calciphylaxis-like skin lesions, pruritus	Skin biopsy
Nerves[e]	Ischaemic neuropathy	Clinical assessment
Muscle[e]	Myopathy by CaOx deposition	Biopsy, CT
Bowel[e]	Prolonged oxalosis: depositions of CaOx in the intestinal wall	CT
Joints[e]	Arthritis (late sign)	X-ray, CT

Cochat et al., Nephrol Dial Transplant 2012

Involvment	Organ	Symptoms	Diagnosis
▪ **Always**	Kidney	•Stones •Medullary or diffuse nephrocalcinosis •Cortical nephrocalcinosis	US, CT (cortical nephrocalcinosis may be missed on US)
▪ **Frequent**	Bone	•Fractures •Bone pain •Growth retardation	X-ray
	Eye	•Disturbed vision •Specific brown colored retinal deposits	Fundoscopy
• **Often**	Arteries	•Media calcifications	US, CT
	Myocardium	•Cardiac failure •Arrhythmia •Heart block •Left ventricular hypertrophy •Systolic and diastolic dysfunction	ECG, echocardiography, CT (calcifications)
	Thyroid	•Hypothyroidism	US, thyroid function tests

Involvment	Organ	Symptoms	Diagnosis
▪ **Less often**	Skin	•(Painful) skin nodules •Skin necrosis •Gangrene •Calciphylaxis-like skin lesions •Pruritus	Skin biopsy
	Nerves	•Ischemic neuropathy	Clinical assessment
	Muscle	•Myopathy by CaOx deposition	Biopsy, CT
	Bowel	•Prolonged oxalosis (depositions of CaOx in the intestinal wall)	CT
	Joints	•Arthritis (late sign)	X-ray, CT

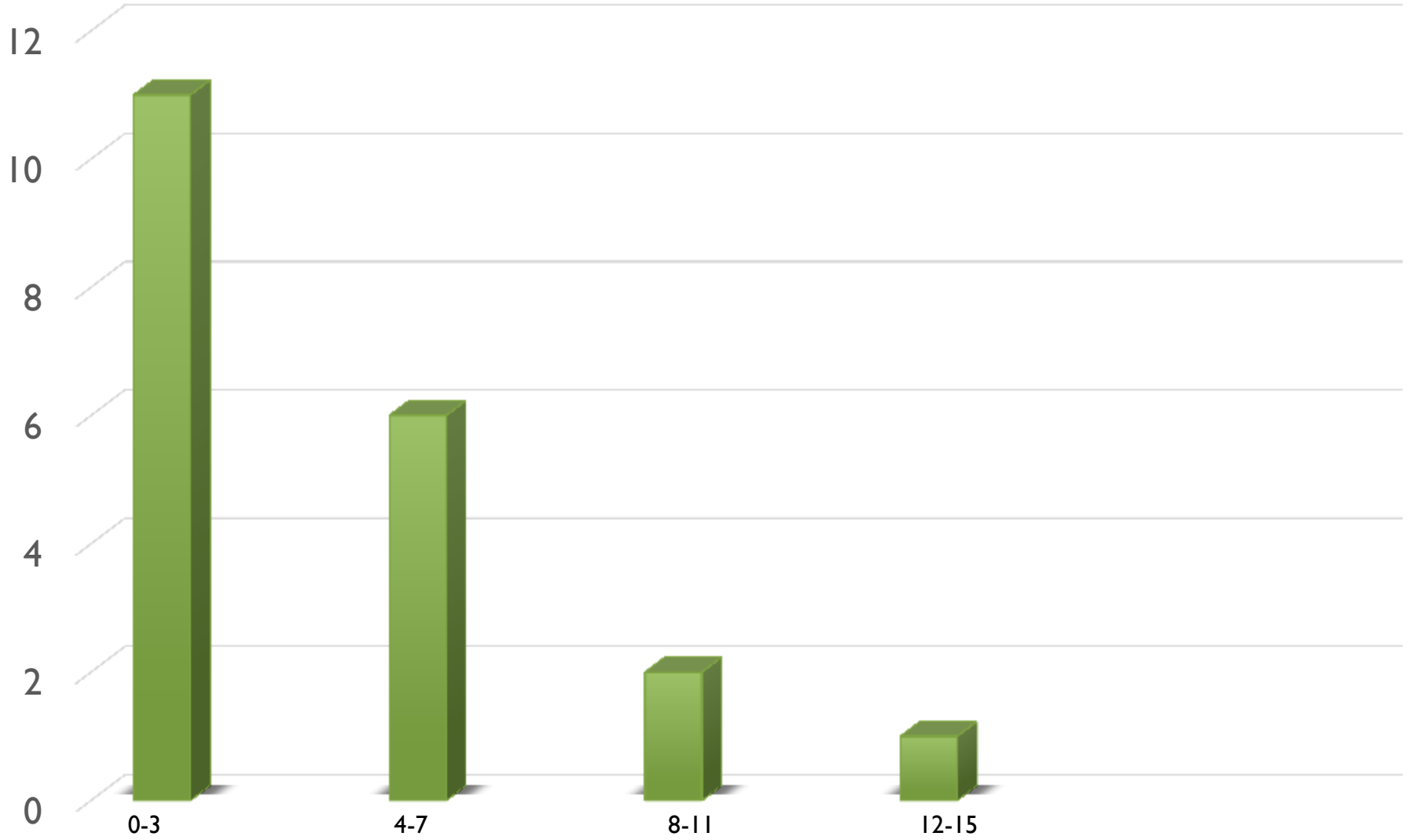


Primary hyperoxaluria diagnostic algorithm

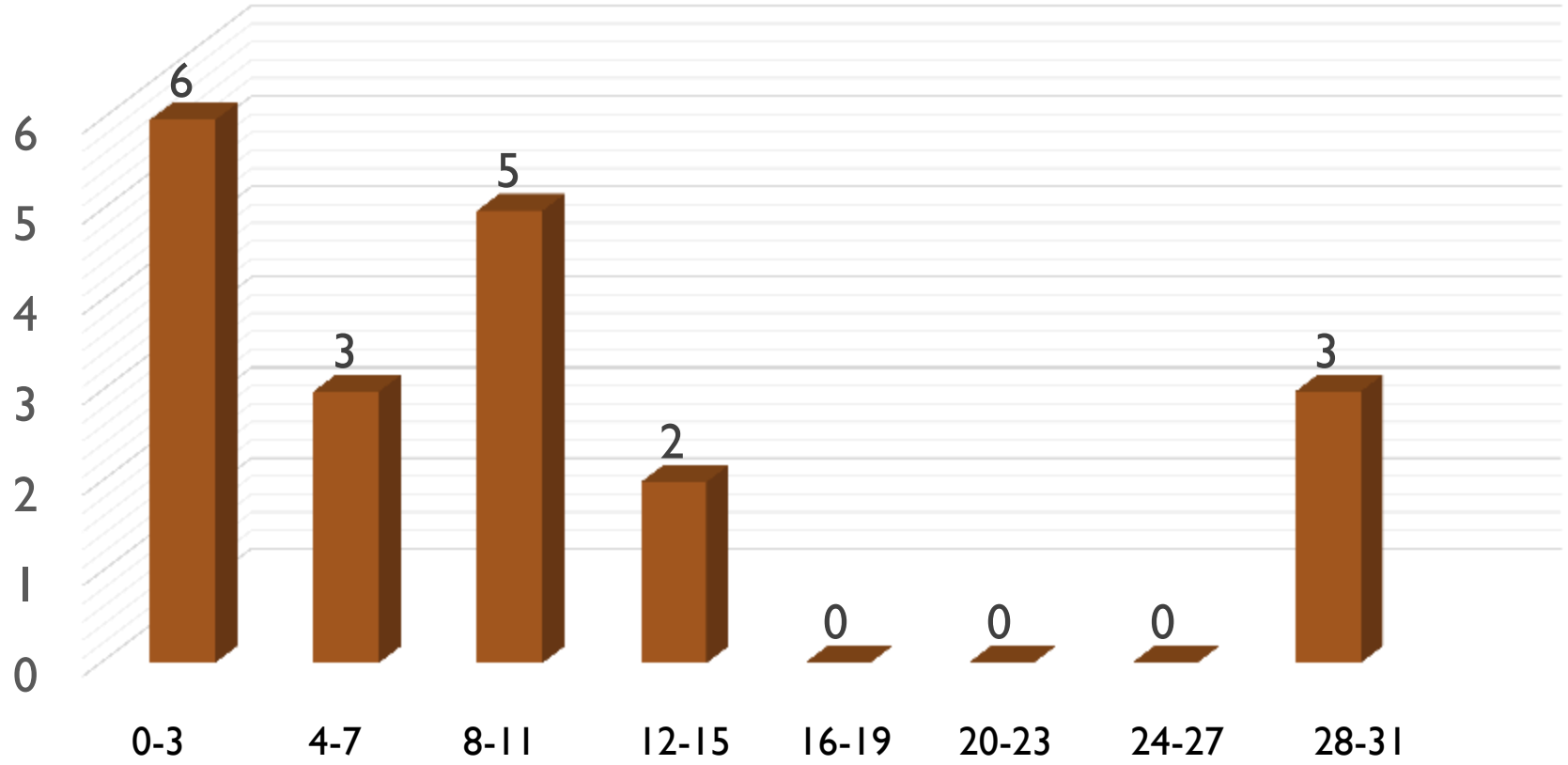
Characteristics of genetically confirmed PH I patients

- Twenty patients/**18** unrelated families
- Consanguinity: **75%**
- Familial: **40%**
- Median age of onset of symptoms: **3 years (range 0.3-16)**
- Median age at diagnosis: **8 years (range 0.3-31)**
- Delay in diagnosis: **0-26 years**

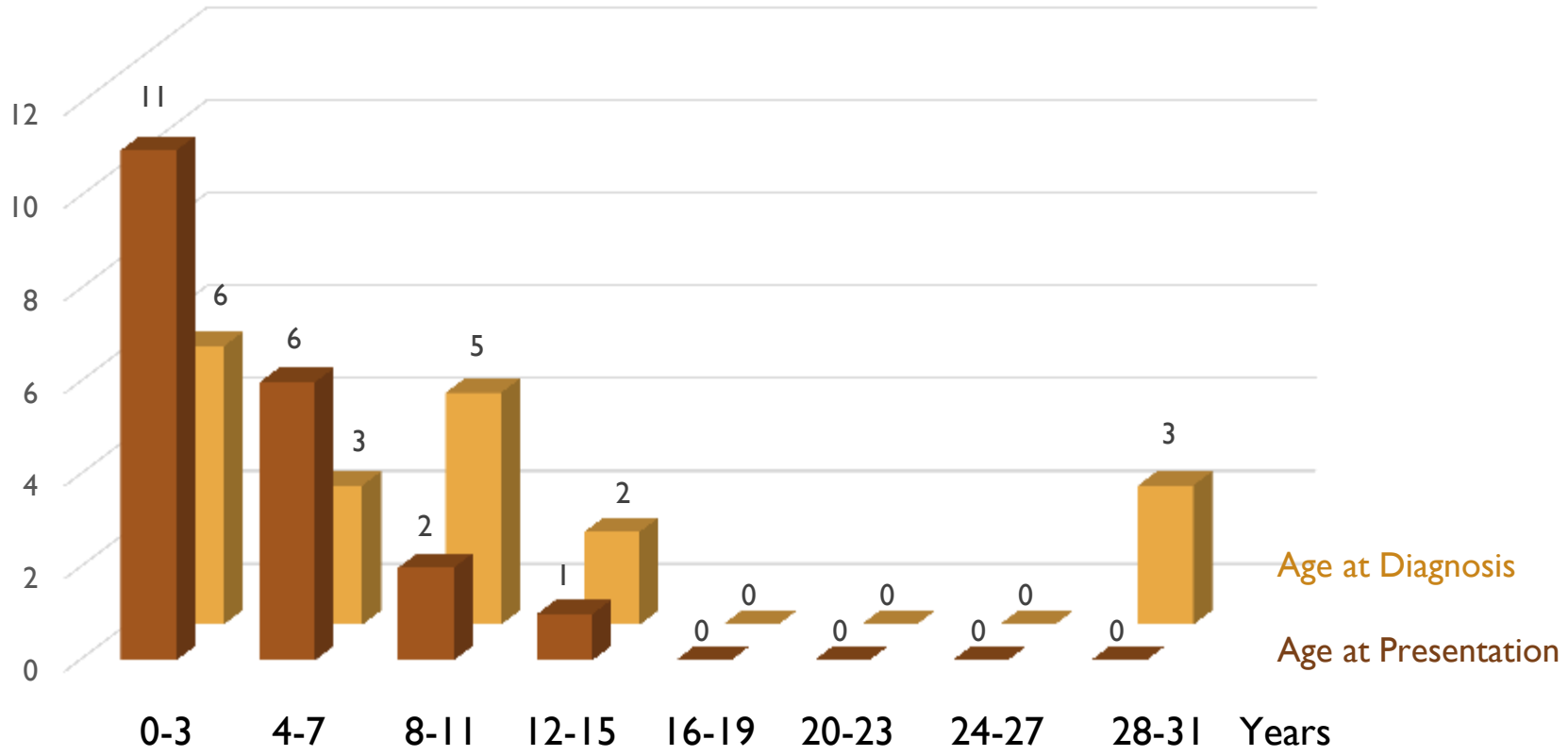
Age of First Presentation in Years



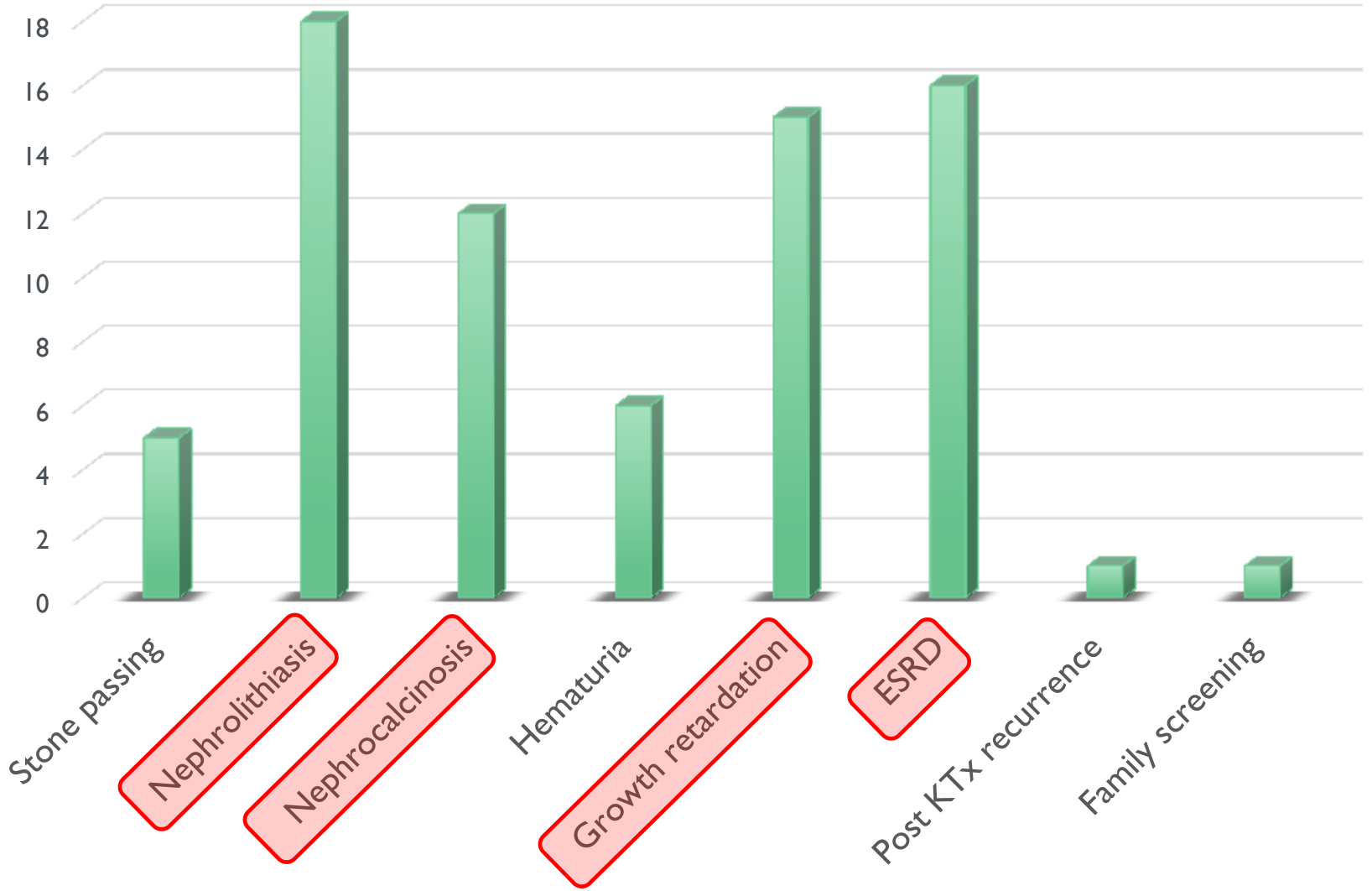
Age at Diagnosis



Age at Presentation/Diagnosis



Symptoms and Findings at Presentation



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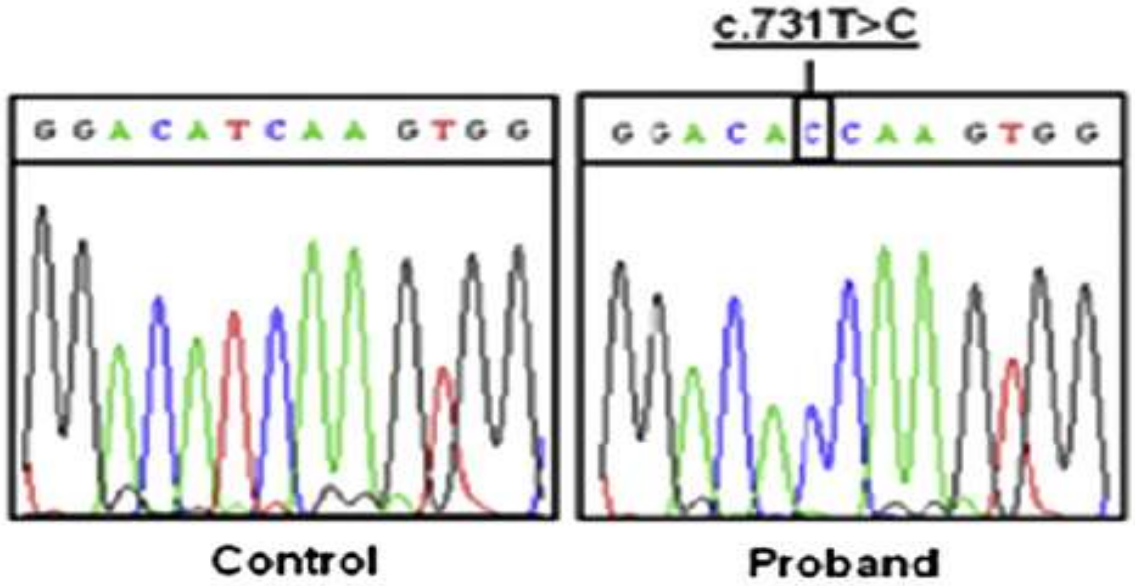
c.731 T>C (I244T) AGXT Mutation

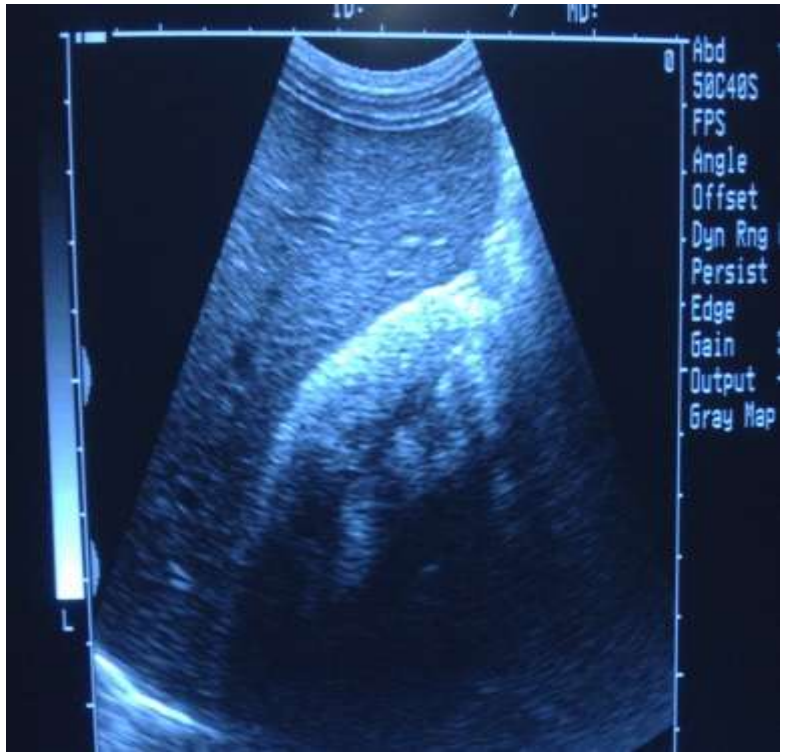


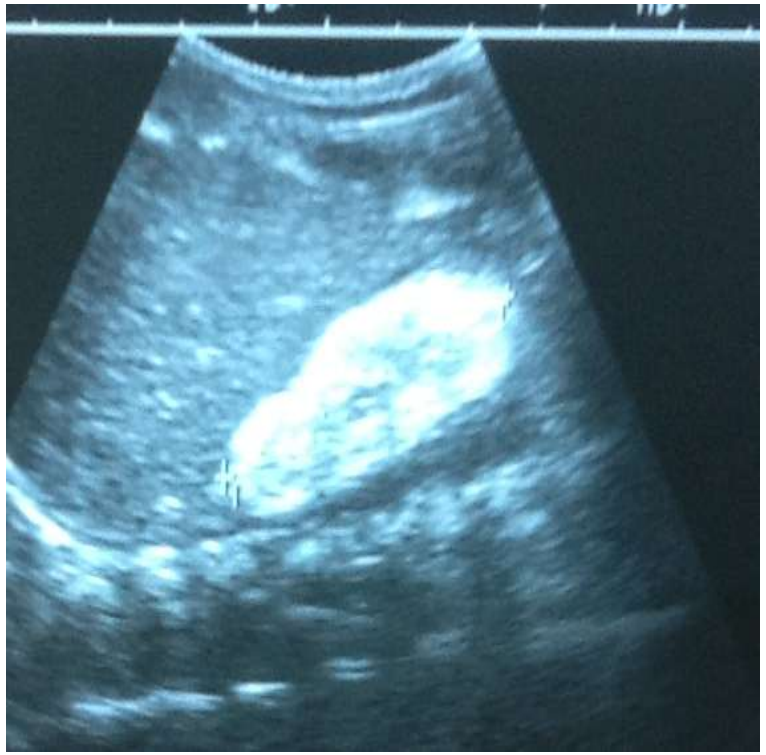
- Most mutations are in a homozygous state, reflecting the high rate of endogamy in our population

CONSANGUINITY: **75%**

INFANTILE PH1

- Three infants 3/20 (15%):
- FTT and ESRD
- Imaging: corticomedullary nephrocalcinosis (few bilateral kidney stones in 1/3)
- Duration between onset of symptoms and diagnosis:
  - 2/3: diagnosed upon presentation
  - 1/3: 3 months delay





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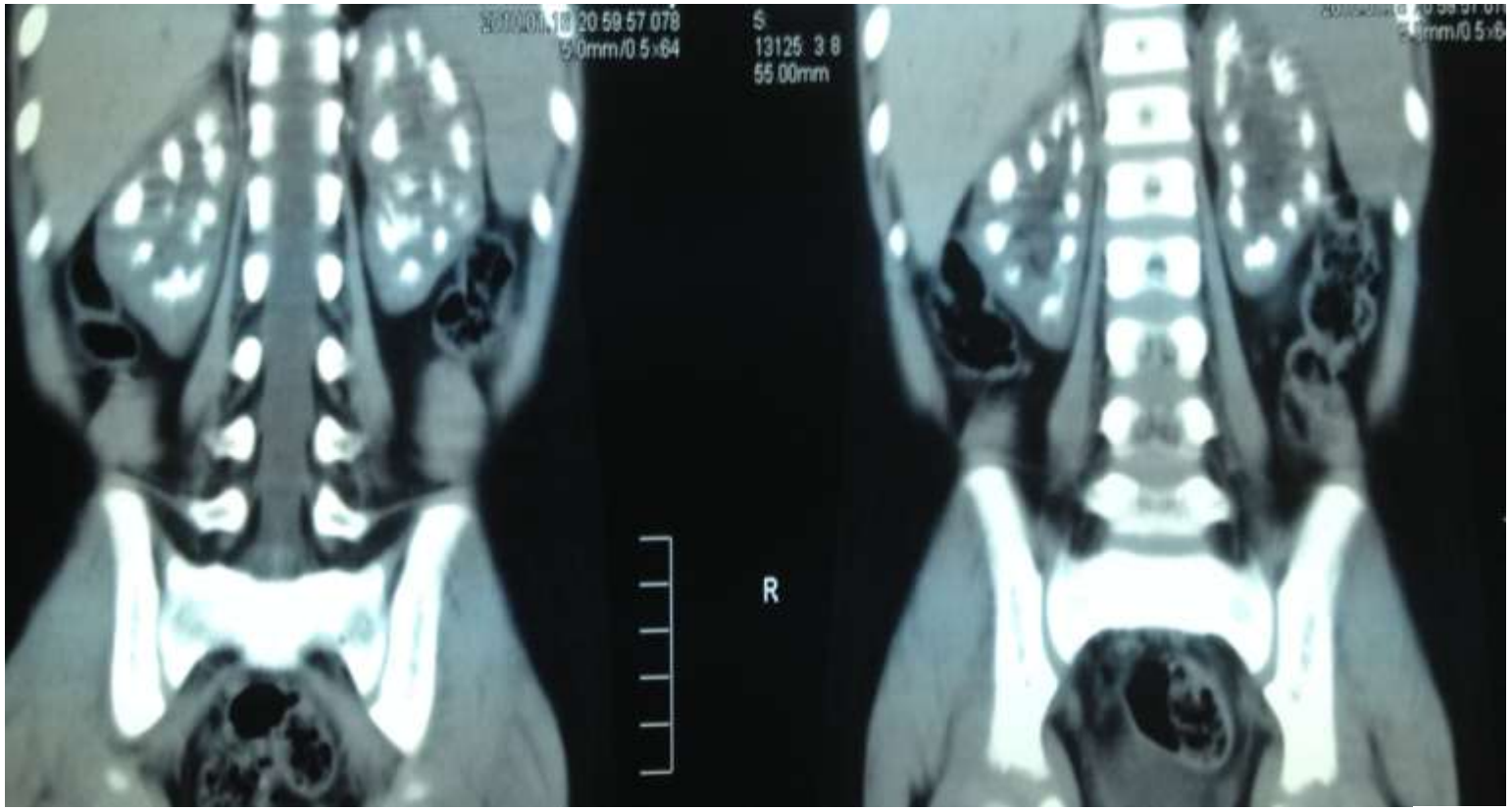

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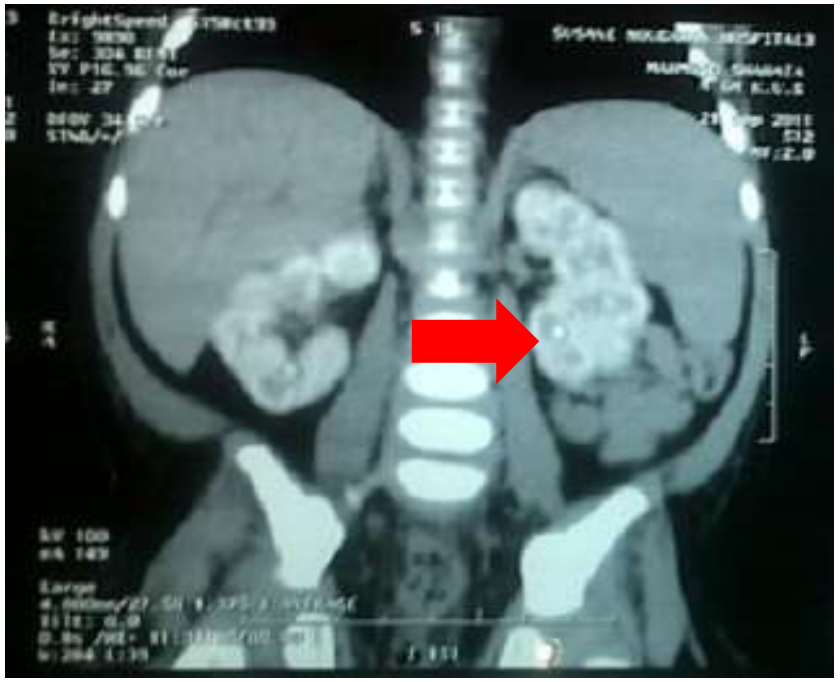

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النادرة

- 28 years old male
- Progressive renal impairment leading to ESRD at the age of 25 years
- Referred as ESRD patient with hyperechogenic kidneys - (ESRD) phenotype
- Unidentified primary renal disease

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- 12 years old male
- Referred as ESRD patient with "hyperechogenic kidneys" - (ESRD) phenotype
- Unidentified primary renal disease

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WHAT IS THE OPTIMUM MANAGEMENT PLAN?

Pre-Tx

Diagnostic evaluation

Pre-Tx work up

Therapeutic intervention

Tx

Tx Strategy

- Donor selection
- Transplantation
- Immunosuppression protocol

Post-Tx

Recurrence

Pre-Tx

No identified Dx

Extent of disease

Room for therapeutic intervention!

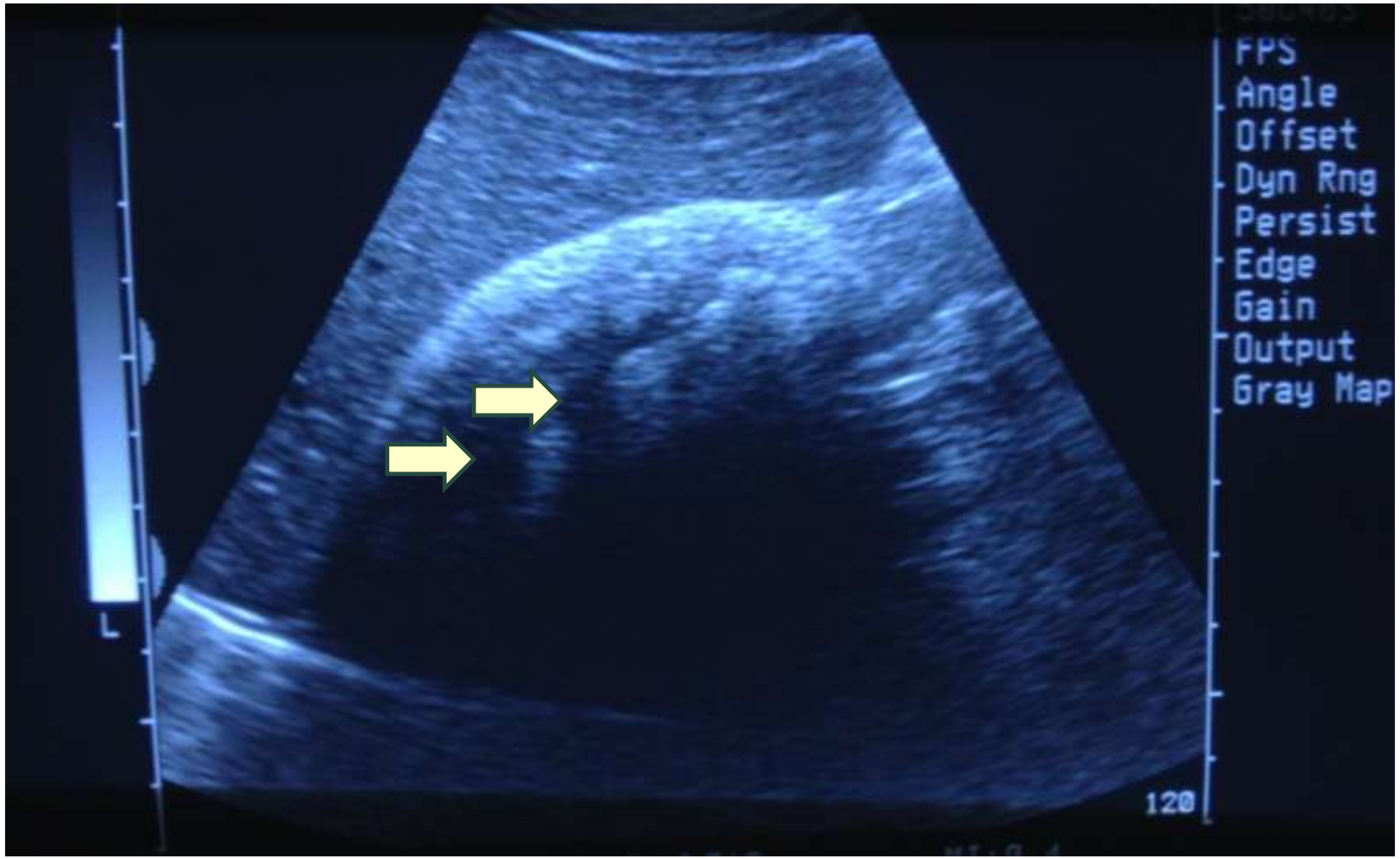
Tx

Tx Strategy

- LRD or LURD
- Kidney alone!
- Immunosuppression protocol!

Post-Tx

Risk of recurrence?



High index of suspicion

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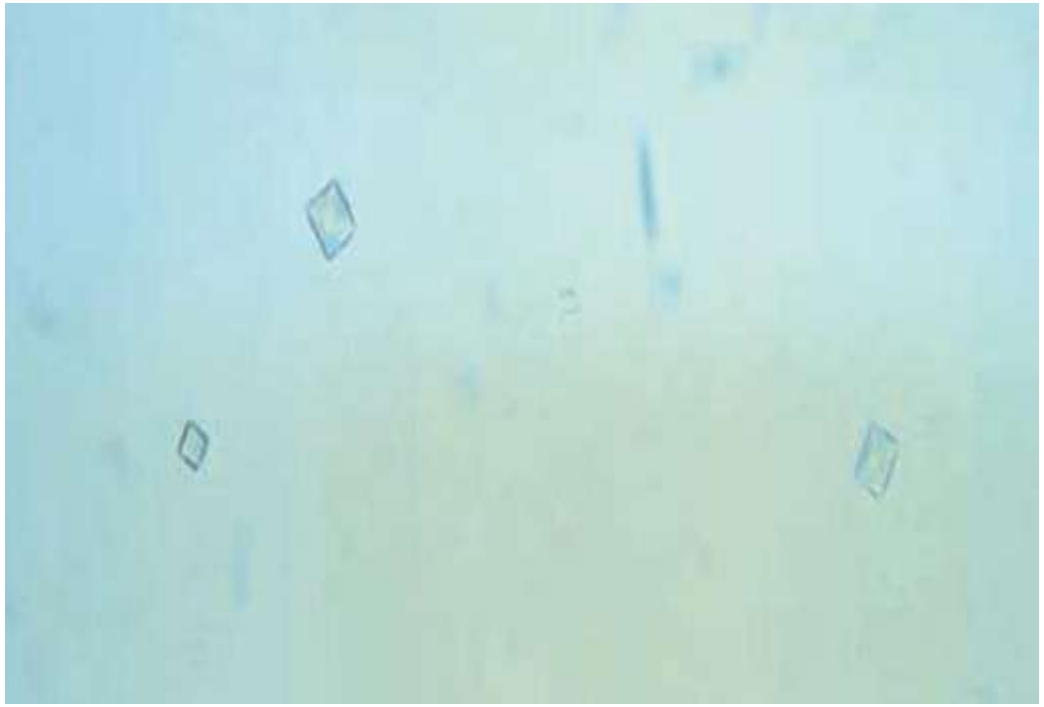
النادرة

DIAGNOSIS

Urine crystals:

Monohydrated calcium oxalate (whewellite)



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- **Urine oxalate**

  > 0.5 mmol/1.73m²/d

- **Uox/Ucr**

Urinary Excretion	Reference Range
24-Hr specimen	
Oxalate, all ages	<45 mg (0.5 mmol)/1.7 m^2
Random ("spot") specimen	
Oxalate:creatinine	
<1 yr	11.9–207 μg/mg (15–260 μmol/mmol)
1 to <5 yr	8.7–95.6 μg/mg (11–120 μmol/mmol)
5 to 12 yr	47–119 μg/mg (60–150 μmol/mmol)
>12 yr	1.6–63.7 μg/mg (2–80 μmol/mmol)

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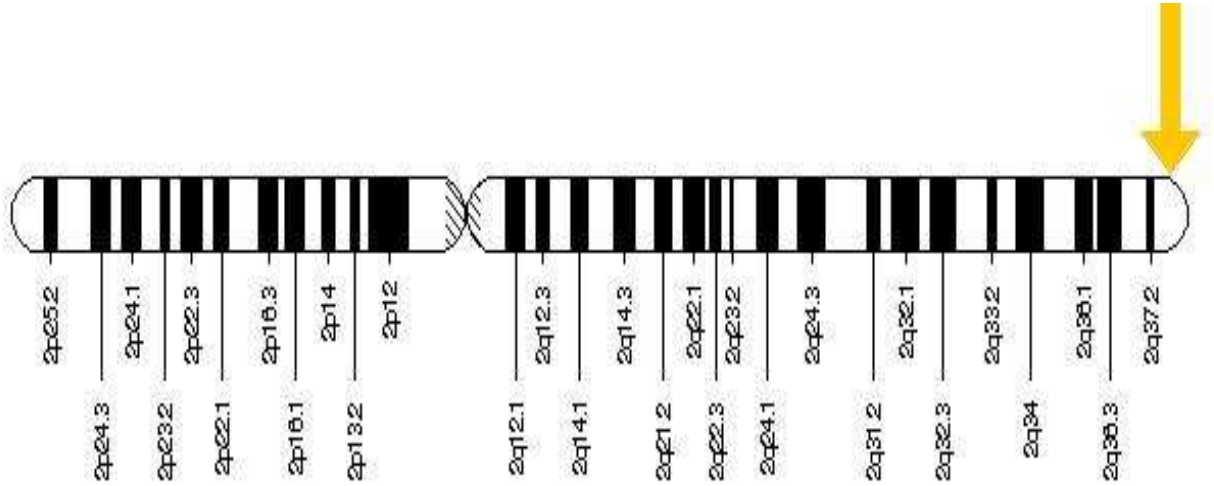
Genotyping

- *AGXT* gene sequencing
- Prenatal diagnosis



Pediatr Nephrol (2005) 20:555–557
DOI 10.1007/s00467-005-1813-0

EDITORIAL COMMENTARY

Ernst Leumann · Bernd Hoppe

Primary hyperoxaluria type 1: is genotyping clinically helpful?

- **Plasma oxalate** N < 5 µmol/L

  Limited value for diagnosis

- **Enzyme activity** Liver biopsy: limited indications

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SUPPORTIVE MEASURES

- High fluid intake ≥ 3 L/m² per 24 h
  - Tube feeding for adequate hydration (infants)
- Vitamin B6 (pyridoxine)
  - Starting at a dose of 5 mg/kg, up to 20 mg/kg per day
  - Aiming to decrease Uox by < 30% (pyridoxine sensitivity)
- Calcium oxalate crystallization inhibition
  - Oral potassium citrate
  - 0.10–0.15 g/kg BW per day as long as GFR is preserved

No special dietary interventions in the absence of CKD

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SURGICAL MANAGEMENT OF UROLITHIASES

- **Avoid any kind of surgical intervention** in patients with uncomplicated urinary stone disease, except when there is obstruction, infection or multiple stones

- **Mini-invasive endoscopic (laser) procedure** is the preferred strategy in patients who require intervention

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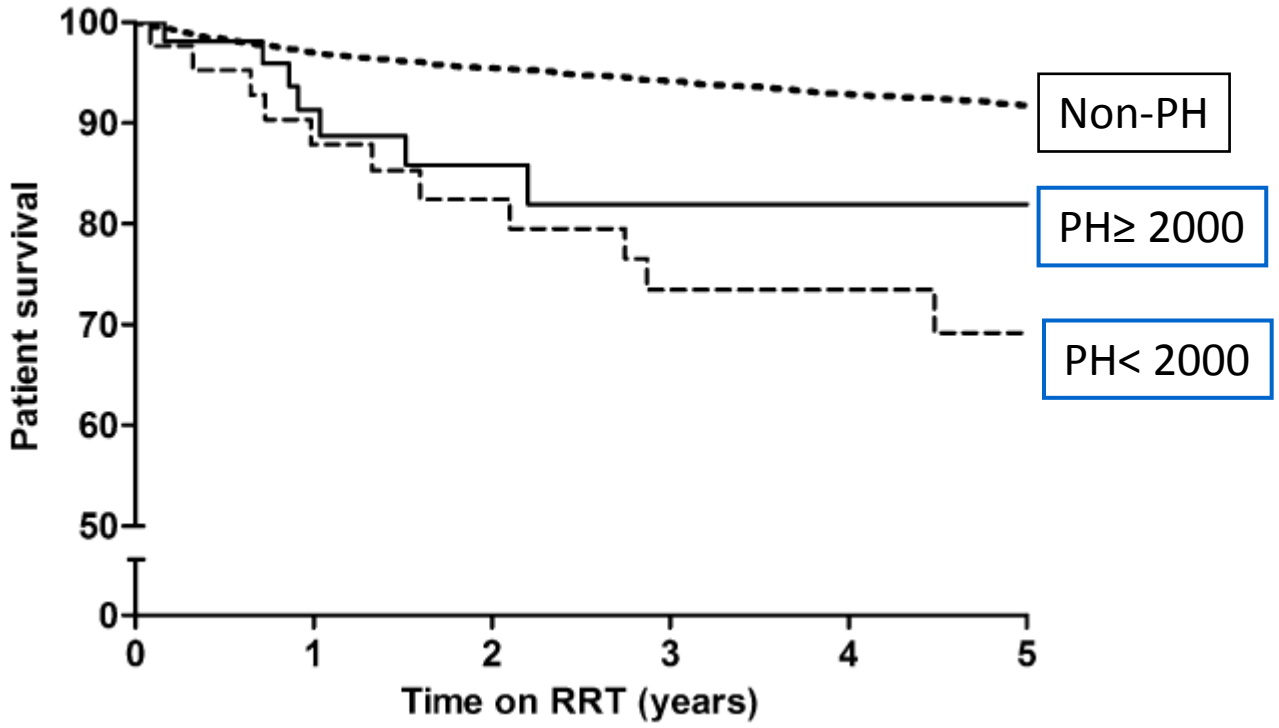
RRT: UNADJUSTED 5-YEAR PATIENT SURVIVAL



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DIALYSIS

Systemic deposition as soon as Pox > 40 to 50 µmol/L

- Conventional HD

Oxalate production
by the liver
4 to 8 mmol/day

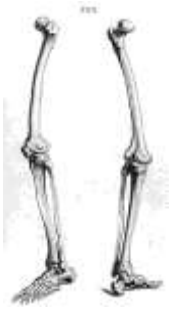
- Daily HD
- Nocturnal dialysis
- Combination HD + PD

50%

50%

25%

75%



Isolated kidney transplant	Early: not appropriate due to the uncertainty of renal deterioration in slowly progressing cases. If there is rapid renal deterioration or the patient is on dialysis, the best option is dual transplantation. It may be considered in cases of slow renal deterioration, usually in older patients.
Simultaneous liver-kidney transplant	The best option in patients with advanced renal failure or on dialysis. It should be carried out at the earliest possible stage (GFR 15-20ml/min). The donor must obviously always be deceased.
(Split) partial liver transplant	Not recommended, due to the liver's excess residual oxalate production. Transplantation would be from a living donor and would be carried out using one of 3 methods: partial liver (when GFR >15-20ml/min), simultaneous liver-kidney or sequential liver-kidney. Consider in exceptional and critical situations.
Isolated liver transplant	Ideal when there is not yet advanced renal failure (GFR >20ml/min) in young adults or children.
Sequential liver and kidney transplant	This option requires two donors, but it is less aggressive from the surgical perspective. If GFR >15-20ml/min, the option is liver first and assessment of subsequent kidney progression. If GFR <15-20ml/min, the option is kidney first. Consider in cases of advanced kidney damage but with very slow progression.

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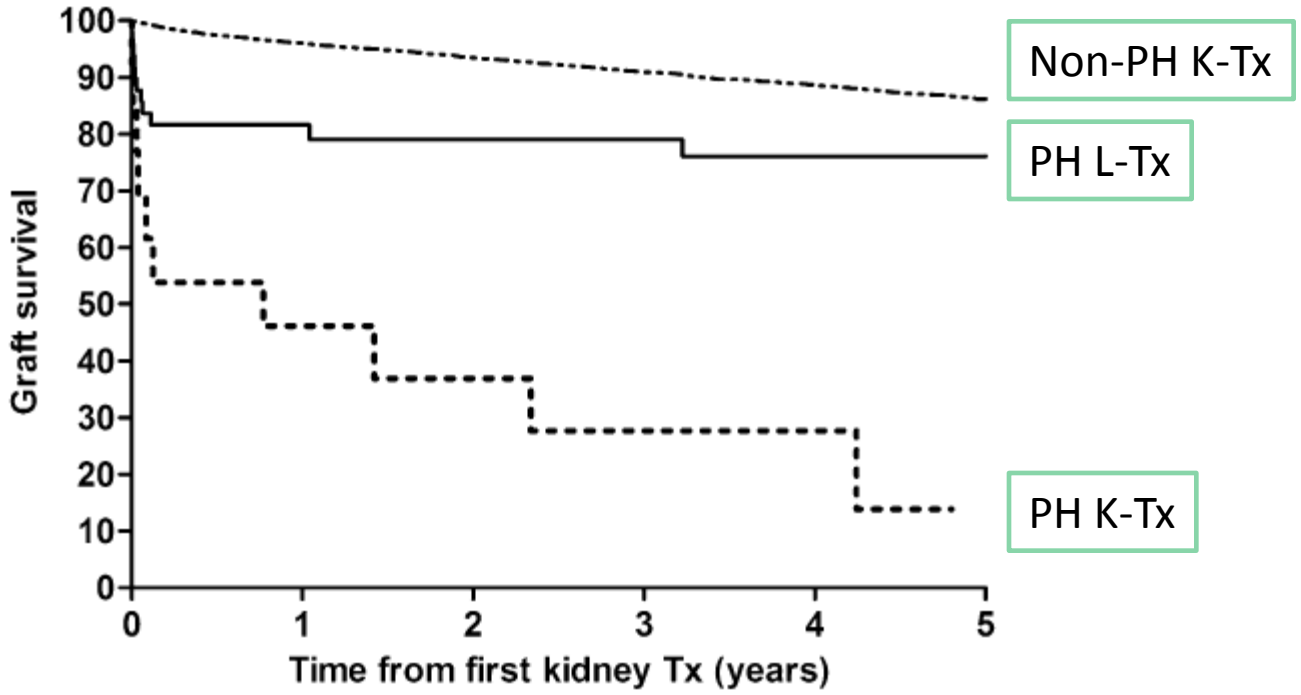

UNADJUSTED 5-YEAR KIDNEY GRAFT SURVIVAL

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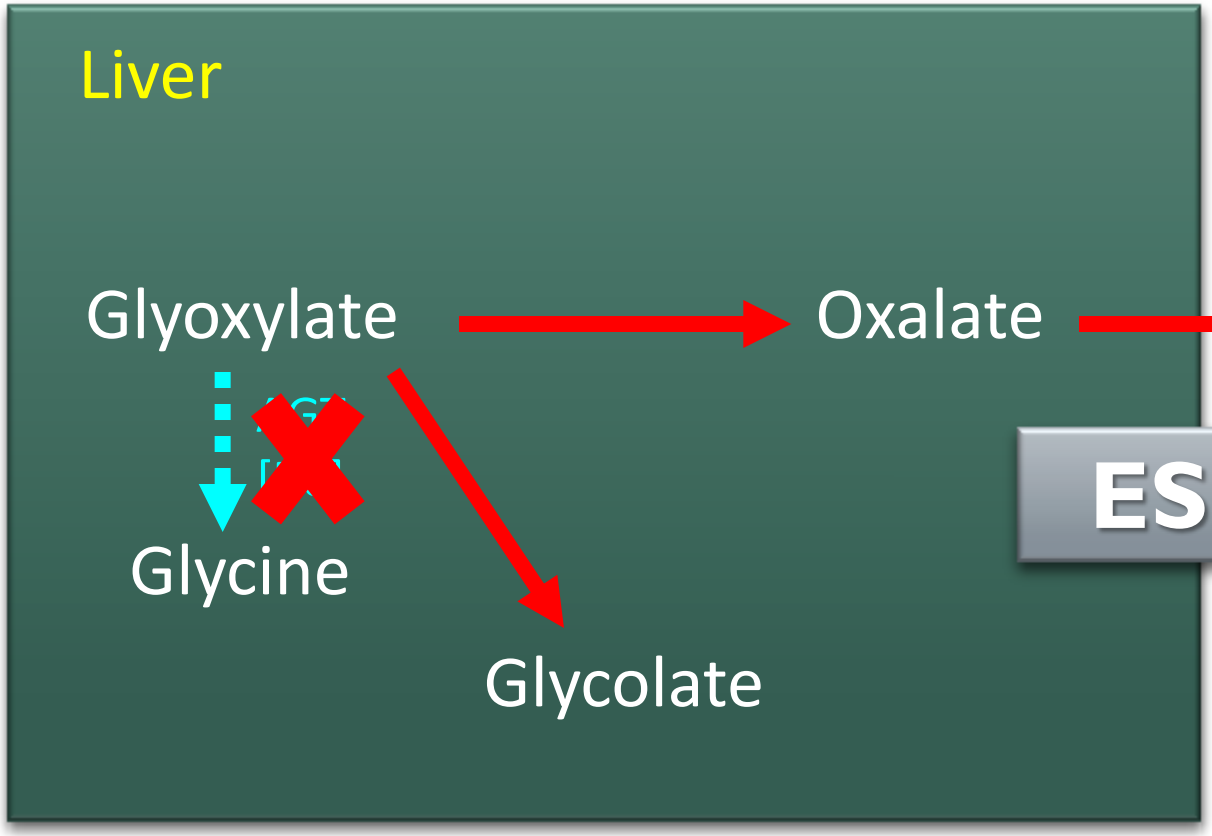
Clinical phenotype, genotype, and graft survival of combined liver and kidney transplanted PH1 patients

EGORD #	Family #	Gender	Age of onset (Yr)	Age at Dx (Yr)	Stones	NC	Graft survival (Yr)
01.05.10/PH	1	M	3	3.5	Numerous	CM	5
02.10.10/PH	2	F	7	10	Numerous	0	4
08.09.11/PH	8	M	5	6	Few	CM	2

Healthy

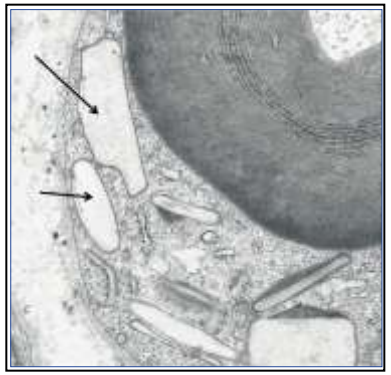


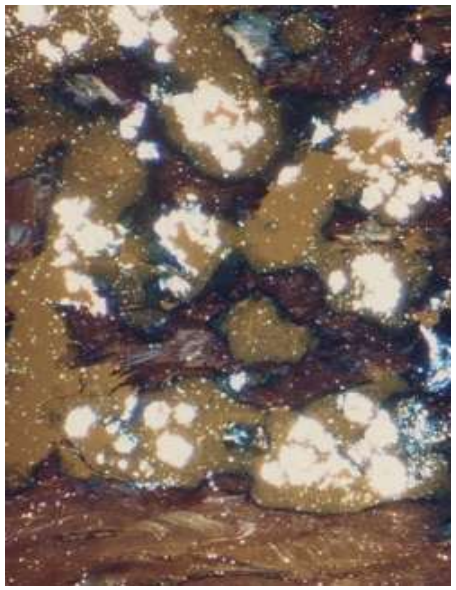
Plasma

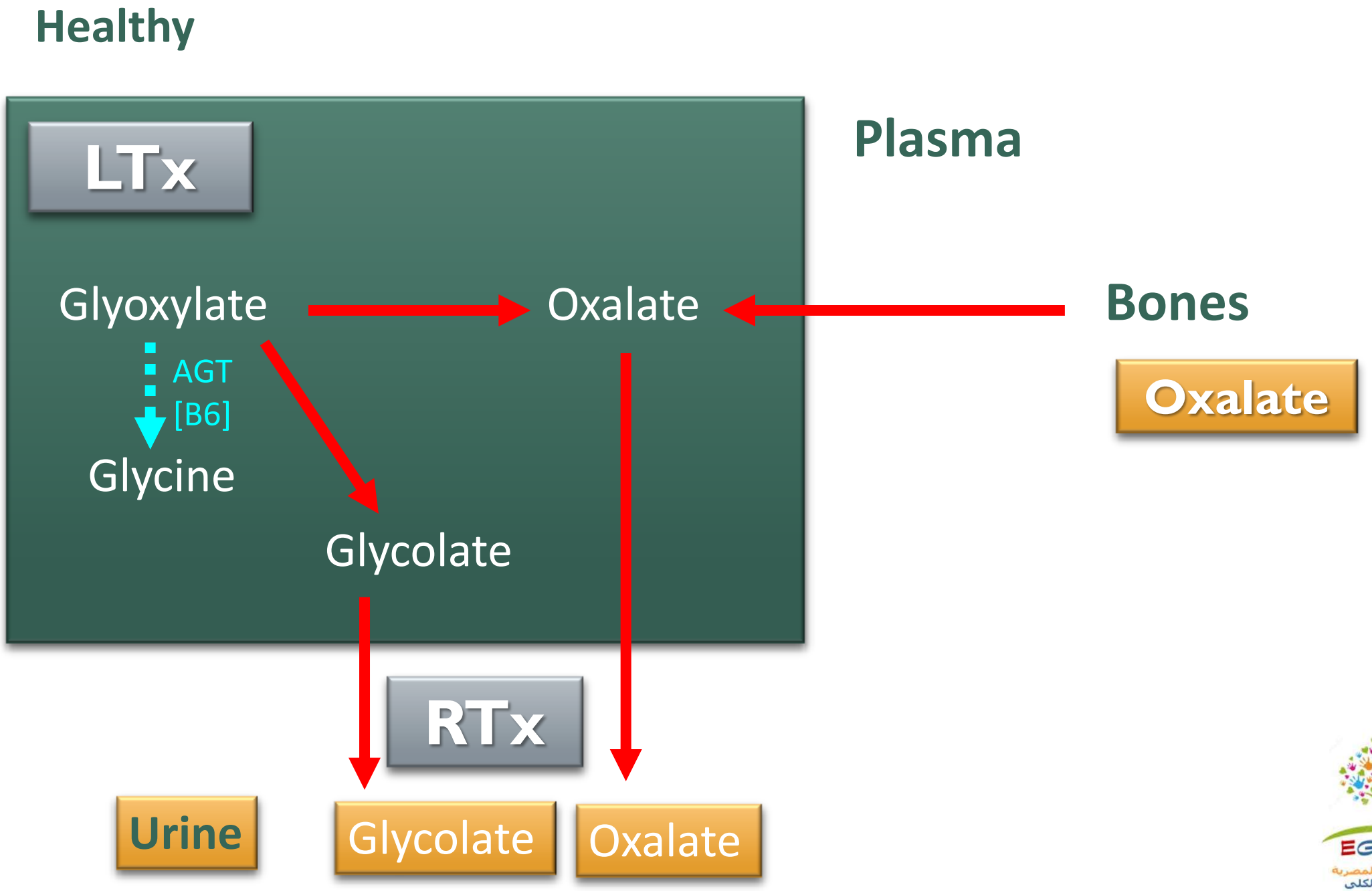
ESRD

Bones

Oxalate






Healthy
LTx
Plasma
Glyoxylate
Oxalate
Bones
AGT
[B6]
Glycine
Oxalate
Glycolate
RTx
Urine
Glycolate
Oxalate

Suggested Tx options

according to residual GFR, systemic involvement and local facilities

Tx strategy	Simultaneous liver + kidney	Sequential liver–kidney	Isolated kidney	Isolated liver
CKD Stage 3 (30 < GFR < 59)				Expert opinion
CKD Stage 4 (15 < GFR < 29)			Gly170Arg Phe152Ile	
CKD Stage 5 (GFR < 15)		+++	Gly170Arg Phe152Ile	
Infantile form (ESRD < 2 years)		+++		
HD strategy	**Perop + postop according to POx and GFR**	**Standard HD following liver Tx aiming at POx < 20 µmol/L**	**Preop + perop**	**Sometimes peroperative**

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CONCLUSIONS

- Highly consanguineous cohort
- Phenotypic heterogeneity and intrafamilial variability
- Majority homozygous mutations
- Genetic heterogeneity: 12 different *AGXT* mutations
- Three out of 12 mutations were identified in 62% of studied families

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CONCLUSIONS

- **Priorities**
  - Think of PH
  - Early supportive measures ASAP
  - Patient/family counseling regarding lifelong management
- **Management of PH requires technical and ethical resources**
- **Various treatment options may help in the future**

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Egyptian Society of Pediatric Nephrology & Transplantation (ESPNT)
The 3rd Inherited Kidney Diseases Workshop (IKDW3)

ASN 2015

Time	Min	Topic	Presenter/Moderator
12:45-12:50	5	Introduction-Overview of Program Update from RKSC/RDCRN	Dr. Milliner
12:50-1:00	10	Overview of RKSC Protocols (All 4 diseases) • Registry • Biobank • QoL	Dr. Milliner
1:00-1:05	5	International registry opportunities with OHF	Ms. Kim Hollander
1:05-1:20	15	Guest Speaker Title: Primary hyperoxaluria type I in Egypt: clinical phenotypes and mutational spectrum of the *AGXT* gene	Dr. Soliman
1:20-1:30	10	ProRKS Protocol • Objectives • Eligibility • Expectations	Dr. Lieske
1:30-1:40	3 7	Pilot Projects/Training Program Overview Pilot project report	Dr. Goldfarb Dr. Langman
1:40-1:45	5	Discussion and Closing Comments	Dr. Milliner

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